

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
CHLOROTHALONIL

Chemical Code # 677, Tolerance # 275, SB 950 # 033

Original Date: June 23, 1987

Revised 1/7/88, 1/30/89, 5/9/89, 10/05/89, 6/6/90, 10/11/91, 10/6/94, 5/17/95,
6/21/95, 7/26/95, 10/20/95, 1/11/96, 4/21/97, 8/21/97, 2/17/98, 8/17/06, 10/27/06

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required, however a 3-month rat neurotoxicity is acceptable, with no adverse effects

Toxicology one-liners are attached.

All relevant record numbers through 227393 (Document No. 275-458), and all relevant 900000-series studies have been examined. This includes all records on file at DPR as of 10/24/06. Aldous, 10/27/06.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: t20061027.wpd

Revised by Moore, 8/17/06; and subsequently by Aldous, 10/27/06.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

Both chronic and oncogenicity study data gaps are filled. There are several studies listed under both headings.

CHRONIC TOXICITY, RAT

Four chronic rat studies were reported during the period 1967 to 1970. In addition, a 1978 Gulf South Research Institute oncogenicity study was submitted, and two rat oncogenicity studies compatible with current oncogenicity study guidelines were subsequently completed. Of the latter two studies, the 1985 IRDC study (Volumes 100-104) was accepted to fill the oncogenicity study data requirement, and the subsequent study in Vol. 164 provided limited ophthalmology and a NOEL for the most sensitive treatment effects. Additional shorter term studies have been submitted, which have some relevance in understanding possible chronic effects. Collectively, the array of rat chronic, oncogenicity, and subchronic studies adequately address the rat chronic and oncogenicity requirements of DPR (i.e. data gaps are filled). No essential new information is likely to be gained by initiating further rodent chronic studies, with the possible exception of oncogenicity mechanistic studies, if desired (see "ONCOGENICITY, RAT" section below). C. Aldous, 10/4/89, 7/21/97.

040 941874 "Two-Year Dietary Administration - Rats. Daconil-2787 (Technical) Final Report." (Hazleton Labs., 6/26/70) Chlorothalonil (purity not given) at 0, 4, 10, 20, 30, 40 or 60 ppm in the diet to 50 rats/sex/group. Possible adverse effect: renal tubular vacuolization and hypertrophy. Systemic NOEL = 30 ppm. Incomplete. Unacceptable: histopathology incomplete in number of animals, deaths during the study, and reports; test article and treated feed not characterized; too few animals continued to 2 years; missing diet analysis. Christopher 3/15/85, Davis 12/2/86.

115 035818 (K. L. Stemmer, University of Cincinnati, 6/19/70) Letter and report evaluating chronic rat study (040 941874). Dr. Stemmer contests the nephrotoxicity reported in the study and concludes that there is no toxicity. CDFA reviewer did not change the possible adverse effect conclusion. Apostolou 12/6/85, Davis 12/2/86.

275-263 143376 Duplicate copy of 040:941874, preceded by Dr. Stemmer's letter of 6/19/70 (see 115:035818, above).

039 941898 “Statement and Evaluation of Kidney Histopathology of Daconil 2787 in Rats and Dogs” by Dr. Klaus Stemmer, University of Cincinnati. (6/19/70) Stemmer concludes there is no nephrotoxicity in either study; presents experimental evidence for artifactual basis of anomalies in the rat study. Analysis of other rat studies shows histological kidney alterations at higher doses. NOEL < 500 ppm. In summary, it is not nephrotoxicity in rats at issue, but rather the dose level. CDFA agreed that there is no nephrotoxicity in the dog study, but found positive evidence in the rat study. Davis 12/2/86. EPA ONE-LINER (040 941874): Systemic NOEL = 60 ppm (HDT). Oncogenic NOEL > 60 ppm. Levels tested = 0, 4, 10, 20, 30, 40 and 60 ppm. CORE GRADE = Not stated

129 050480 “Two-Year Dietary Feeding - Rats. Final Report.” (Hazleton Laboratories, Inc., Project No. 200-148, 1/20/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 35 rats/sex/group at 0, 0.15, 1.5, or 3.0 % by weight for up to 104 weeks. One interim kill for three groups, with two interim kills and termination at 47 weeks for the high dose group. Possible adverse effect: dose-related reductions in body weight gain and food efficiency; elevated kidney weights; liver weight changes; histopathological changes in the thyroid, stomach, kidney and liver. NOEL < 0.15%. Incomplete. unacceptable: dose levels too high; changes in dose level during the experiment; lack of information on test material; no feed analysis; excessive mortality; insufficient observations, serum chemistry, necropsies, ophthalmology, and histopathology; and missing data. Davis, 5/8/87. EPA ONE-LINER: Systemic NOEL = 0.15% (LDT). Systemic LEL = 1.5%. Depression of growth, kidney nephritis. CORE GRADE = Not stated

N.B. The following two chronic feeding studies (Records 050891 and 050892) are supplementary to the previous study (Record 050480) and therefore not guideline studies.

129 050891 “Two-Year Dietary Feeding: Rats. Final Report.” (Hazleton Laboratories, Inc., Project No. 200-154, 4/12/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 35 rats/sex/group at 0 or 0.5 % by weight for 104 weeks. Interim kills of 5/sex/group at weeks 13 and 52. Possible adverse effect: Reductions in body weight gain and food efficiency in both sexes; some reduced coagulation times in females; elevated kidney/body weights and liver/body weights; kidneys enlarged, abnormal in color, and showing some cyst-like foci or large cysts; dilatation of the cecum; histopathological degeneration in kidneys. NOEL < 0.5%. Supplementary study: single dose level; lack of information on test material; no feed analysis; excessive mortality; insufficient observations, serum chemistry, necropsies, ophthalmology, and histopathology; and missing data. Davis, 5/11/87. EPA ONE-LINER: Systemic NOEL less than 0.5% (single dose tested). Kidney hypertrophy. CORE GRADE = Not stated

129 050892 “Long Term (76 Weeks) Feeding Study: Rats. Final Report.” (Hazleton Laboratories, Inc., Project No. 200-175, 8/16/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 15 rats/sex/group at 0, 0.05, or 0.1 % by weight for 76 weeks, or 0.5 % by weight for 23 weeks (interrupted for 13 days). Interim kills of 5/sex/group at week 20. Possible adverse effect: Reductions in body weight gain and food consumption; decreased survival; elevated kidney weights and ratios and cecum weights; kidneys enlarged, abnormal in color, and showing a rough or pitted surface; histopathological degeneration in kidneys. NOEL = 0.05% for 76 weeks. Supplementary study: lack of information on test material; no feed analysis; too few animals; test period too short; insufficient observations, hematology, serum

chemistry, urinalysis, necropsies, ophthalmology, and histopathology; and no data tables. Davis, 5/12/87. EPA ONE-LINER: Systemic NOEL < 0.05% (LDT). Growth depression, tubular hypertrophy. CORE GRADE = Not stated

COMBINED, RAT (SUPPLEMENTARY DATA, NOT USING CHLOROTHALONIL)

070 025237 “Summary of DS-3701 Toxicology Studies: Chronic Toxicity and Tumorigenicity/DS-3701 Rat Study” Document No. 100-5TX-80-0016-007; Lab and report date not stated; 18-month interim report of 24-month feeding study with 4-hydroxy-2,5,6-trichloroisophthalonitrile (DS-3701, a chlorothalonil metabolite); dose levels of 0.5, 3.0, 15, or 30 mg/kg/day with the two highest levels reduced or dropped during the study. Reversible toxicological effects (unspecified). No tumorigenicity. Systemic NOEL = 3.0 mg/kg/day. Supplementary study: one paragraph summary of study with a related compound. Davis 12/3/86.

SUBCHRONIC: RAT (SUPPLEMENTAL)

275-316 159184 Mizens, M., “A 90-day pilot study for the evaluation of cell proliferation in the kidneys of male rats following the oral administration of technical chlorothalonil,” Ricerca, Inc., 9/26/96, Document No. 6704-96-0010-TX-003. Male F-344 rats were dosed continuously in diet with 0 or 175 mg/kg/day chlorothalonil. Fourteen/group were sacrificed at day 7, and 7/group were sacrificed on days 28 and 91, respectively. Primary objectives were to examine kidney proximal tubular epithelial cell proliferation as evidenced by uptake of BrdU, which was administered by osmotic pump for 3.5 days before respective day of sacrifice. Kidney tissues were examined by H & E staining and by immunohistochemical staining (toward BrdU). The proximal convoluted tubular epithelium underwent degeneration and hyperplasia in treated rats, and tubules were commonly hypertrophied. These changes were evident in the presence of heavy immunohistochemical staining, suggesting that considerable cell proliferation occurred in association with the histopathology lesions. The strong association between proliferation and histopathology is consistent with, but does not prove that a threshold phenomenon was in force. Forestomach lesions consisted of hyperkeratosis and hyperplasia of the squamous epithelium, often with submucosal edema, erosions, and ulcerations. Histopathology in both organs persisted from day 7 to the end of the study on day 91. This is an acceptable ancillary study, with minor deficiencies, as noted in the review. Aldous, 1/29/98.

275-317 159189 Hironaka, M., “Analysis of hyperplastic changes in the stomach and kidney of male rats after 28-day induction by chlorothalonil technical,” Center for Safety Assessment of Food, Agricultural Chemicals and Medicinal Drugs (Japan), 9/25/96, Test # 2913 (063-002), Report No. 3561. F-344 male rats were dosed with 0, 1.5, 15, or 175 mg/kg/day chlorothalonil in diet for 7, 14, 21, or 28 days (6 rats per dose/time combination). Primary objectives were to evaluate forestomach and kidney histopathology and cellular proliferation. Kidney sections were stained with PC10, which contained an antibody to proliferating cell nuclear antigen (PCNA). Forestomachs were evaluated by BrdU immunostaining. Rats were administered 0.1 g/kg BrdU 1 hr before autopsy. A stain attached to BrdU monoclonal antibody was used to visualize tissue uptake of BrdU. Additional sections of both tissues were stained with H&E. Increased labeling indices were observed to some extent at 15 and substantially at 175 mg/kg/day in kidney and forestomach. Responses generally decreased over time in kidney proximal tubular epithelial cells at both of these dose levels, and increased over time

for forestomach in the 15 mg/kg/day group. Neither histopathology nor evidence of cellular proliferation was seen at 1.5 mg/kg/day in either tissue. This study shows that dose levels previously shown to elicit tumors in these tissues also increased cellular proliferation. No such proliferation was seen at 1.5 mg/kg/day, which was below the level which produced tumors in these tissues. Aldous, 2/17/98.

275-316 159181 An interpretive summary of records 159184 and 159189, above. No worksheet.

129 050893 "4-Month Dietary Toxicity Study: Rats. Chlorothalonil. Final Report." (Bio/Toxicology Research Laboratories, Inc., Project No. 24-201, 9/4/75). Chlorothalonil (purity unknown) fed to 15 rats/sex/group at 1, 2, 4, 15, 30, 60, and 120 ppm for 17 weeks. No effects on the parameters examined (growth, food consumption, survival, kidney histopathology). NOEL > 120 ppm for 17 weeks. Supplementary study: The objective of this study was to examine kidney histopathology. Davis, 5/13/87. EPA ONE-LINER: Systemic NOEL = 120 ppm (HDT). CORE GRADE = Not stated

144 059033 "A 90-Day Feeding Study in Rats with Chlorothalonil" (In-Life Phase: IRDC; Histopathology: Experimental Pathology Labs and C.E.R.T.I., France; Supervision: Ricerca, Inc., Sponsor no. 85-0079, 6/8/87) Technical chlorothalonil (97.9%) fed to 90 male rats each at 0 and 175 mg/kg/day with sacrifices of 10 each on days 4 and 7 and at the end of weeks 2, 4, 6, 8, 10, 12, and 13 of treatment. Possible adverse effect: Kidney: vacuolar degeneration in the proximal convoluted tubules epithelium, proximal tubular epithelial hyperplasia, and tubular hypertrophy; Forestomach: gastritis, multifocal ulceration and erosion of the mucosa followed by gross thickening, epithelial hyperplasia and hyperkeratosis. Supplementary study. Davis 10/6/87.

105-8 034368-034371, 034374, 034376, 034377 Wilson, N.H., J. Laveglia, J. C. Killeen, and J. A. Ignatoski, "A Subchronic Toxicity Study of Technical Chlorothalonil in Rats." Primary contract laboratory: Huntingdon Research Centre, England (6/24/83). Document No. 562-5TX-81-0213-004. Technical Chlorothalonil (98% purity) fed at 0, 1.5, 3.0, 10.0 and 40.0 mg/kg/day to 20 rats/sex/group for 13 weeks, at which time half were necropsied and half were continued on an untreated diet for 13 weeks. Satellite groups of 5 rats/sex/dose were necropsied at 6 weeks. Possible adverse effects include increased kidney and liver weights, decreased circulating liver enzymes, tubular hypertrophy and hyperplasia of the epithelial cells of the proximal convoluted tubules, and hyperplasia and hyperkeratosis in the stomach epithelium. There is no NOEL in this dosage range: inclusion bodies were found in tubules of male renal cortex at all dose levels (Record No. 034377). This effect was evidently not associated with toxicologically important changes, hence the NOAEL = 1.5 mg/kg/day for 13 weeks [based on elevated kidney weights, and decreased alanine aminotransferase activity (of questionable toxicological significance)]. Hyperplasia and hyperkeratosis of non-glandular stomach epithelium was elevated at 10 and 40 mg/kg/day. Supplementary study: 034377 is an EM and light microscopic evaluation of kidney tissue. 034374 is a histopathology re-evaluation specifically to evaluate renal tubular hyperplasia. NOTE: Record Nos. 034374 and 034377 were re-examined by C. Aldous in Oct., 1995, and brief additional worksheets were made, indicating conclusions below. Davis, 5/19/87, and Aldous, 10/20/95.

275-108 034374, Wilson, N.H., J.C. Killeen, and J.A. Ignatoski, "Histopathologic re-evaluation of renal tissue from a subchronic toxicity study of technical chlorothalonil in rats (5TX-81-0213)." The report was produced by SDS Biotech Corp., based on evaluations by Dr. W.M. Busey of EPL. Re-evaluation report was dated July 9, 1985. CD rats received 0, 1.5, 3, 10, or 40 mg/kg/day chlorothalonil for 6 wk (5/sex/group), 13 wk (10/sex/group), or for 13 wk with a 13 wk recovery period (10/sex/group). THIS PARTICULAR RE-EVALUATION WAS FOCUSED ON DETERMINING WHETHER A TREATMENT EFFECT WAS PRESENT FOR A CHARACTERISTIC RENAL TUBULAR HYPERPLASIA, WHICH HAD PREVIOUSLY BEEN SHOWN TO CORRELATE WITH RENAL TUMORS. Only males indicated renal tubular hyperplasia in this study. The NOEL for this characteristic renal hyperplasia appears to be 3 mg/kg/day, based on tubular hyperplasia incidences of 0, 1, 0, 2, and 4 in controls through high dose groups, respectively, at the 6-wk sacrifice. (Investigators considered the NOEL to be 10 mg/kg/day, due to the low incidence of hyperplasia at this and lower dose levels). Aldous, 10/12/95

275-107 034377 Wilson, N.H., J.C. Killeen, B.L. Haley, and J.A. Ignatoski, "A Subchronic Toxicity Study of Technical Chlorothalonil in Rats" [Amendment No. 1]. Supplementary report by Huntingdon Research Centre: supplementary study directed by John Colley. ["Amendment 1" date: 11/14/83]. This report includes EM and light microscopy re-evaluations of rat kidney sections, from tissues used in SDS Biotech Corp. Document No. 562-5TX-81-0213-004 (DPR Document Nos. 275-105 to -107). An initial survey of sections by EM revealed elevated incidence and degree of "irregular intracytoplasmic inclusion bodies" in proximal tubule epithelial cells. These bodies were either electron dense (usually amorphous, sometimes needle-shaped) or heterogeneous under EM. These structures, considered to be lysosomal, are common in male rats, but not found in female rats nor in mice. After establishing the treatment effect and characterizing the structures by EM, investigators evaluated sections from all males on study by light microscopy following treatment by Neutral Red, which had been shown to selectively stain the inclusion bodies. Neutral Red analyses found elevated incidence and/or degree of inclusions at all dose levels tested by week 13 (end of dosing phase), with residual changes evident at 3 mg/kg/day and above after a 13-week recovery period. Thus there is no NOEL for these inclusion bodies over this dose range, however the "NOEL" for inclusion bodies remaining after the recovery phase was 1.5 mg/kg/day. Investigators concluded that these bodies were not related to identifiable toxicological lesions in kidneys, including chronic progressive nephropathy. Presence of these inclusion bodies had not been considered previously by CDFA or DPR in setting the overall NOEL for this subchronic study. The NOAEL is 1.5 mg/kg/day, since slightly higher dose levels were associated with "possible adverse effects" (see Record No. 074770). Aldous, 10/16/95.

130, 131, 108 050894-6, 034373 "A 90-Day Toxicity Study of Technical Chlorothalonil in Rats." (Concord Woods Animal Facility, Diamond Shamrock Corporation, 10/19/81). Technical chlorothalonil (98% purity) was fed to 20 rats/sex/group at 0, 40, 80, 175, 375, 750, and 1500 mg/kg/day for 13 weeks. Possible adverse effects include hyperplasia and other morphologic changes of the kidney tubules; altered stools and generally poor physical condition; depressed mean body weights and food consumption; decreased brain, heart, liver, gonad, and kidney weights; altered blood and urine parameters; and focal acute gastritis. NOEL < 40 mg/kg/day for 13 weeks. Toxic effects

were found at all dose levels. Supplementary study. 034373 is supplementary histopathology report. Davis, 5/15/87. EPA ONE-LINER: NOEL < 40 mg/kg/day (relative kidney weights increased at all test levels; urinary vol. and Specific Gravity affected at all test levels). Levels tested-0, 40, 80, 175, 375, 750 and 1500 mg/kg/day in Charles River CD strain. CORE GRADE Minimum

275-297 150595 Mizens, M., "A 21-day repeated dose dermal toxicity study in rats with Technical Chlorothalonil," Ricerca, Inc., Sept. 5, 1996. Document No. 6859-96-0113-TX-002. Ten F-344 male rats/group were dosed dermally in 0.2% aqueous methylcellulose for five days/wk, 6 hr/day, for a 21-day period (i.e. 15 treatment applications). Daily doses were 0, 60, 100, 250, or 600 mg/kg/day of technical chlorothalonil, 98.1% purity, covered by a porous gauze patch. Assessed in-life parameters included body weight and food consumption effects, and clinical observations. At termination, clinical chemistry parameters were assayed, followed by histopathology on kidney, forestomach, and skin lesions. "Application site NOEL" < 60 mg/kg/day: all dose levels showed erythema of treated skin, confirmed by yellow discoloration and desquamation at necropsy, and histological findings of hyperkeratosis, and squamous epithelial hyperplasia and vacuolation. NOEL (exclusive of application site) = 60 mg/kg/day (clinical observations of "rough coat"). Other noted findings were transient body weight and food consumption decrements, small decreases in ALT, and increased kidney weights at 250 mg/kg/day and above (relative to brain weight). There was no associated kidney histopathology. This is an acceptable ancillary study with no adverse effects indicated. Aldous, 11/6/96 (re-evaluated by Aldous on 2/3/98 in consideration of rebuttal comments in Record No. 157407).

275-287 148283 Protocol for Record No. 150595, above, plus U.S. EPA comments on protocol. No DPR worksheet.

275-256 143356 "Histopathologic Evaluation of Kidneys in Male Fischer 344 Rats Following the Oral Administration of Technical Chlorothalonil," (Authors: Gelin, Mark D., and James C. Killeen, Jr.; Ricerca, Inc., Painesville, OH; Lab Report No. 3618-91-0153-TX-002; 12/5/91); Chlorothalonil Technical (Lot No. SDS-2787-0901; purity = 97.2%), dosed as suspensions in 0.5% aqueous methyl cellulose; 0 (vehicle), 40, 80, 175 mg/kg/day for two days; 6 males/group; terminated 16 h after the last dose; Histopathology (kidneys) - epithelial vacuolation (minimal to moderately severe), incidence and severity were dose-related in all treatment groups; epithelial degeneration in proximal convoluted tubules (minimal to moderate) in high-dose group only; Supplemental. (Duncan, 1/29/96)

275-194 133338 Ford, W. H. and Killeen, J.C. Jr., "A 90-day study in rats with the monogluthathione conjugate of chlorothalonil," IRDC (in-life phase), 3/3/87. IRDC Project ID# 293-143. Approximately equimolar amounts of technical chlorothalonil (75 mg/kg/day, purity 97.9), or the monogluthathione conjugate [S-(2,4-dicyano-3,5,6-trichlorophenyl)-glutathione] (150 mg/kg/day, 92.5% purity), or control vehicle (0.5% methylcellulose) were administered by gavage daily for 90 days to 15 male F-344 rats/group. The primary purpose was to investigate whether kidney toxicity was associated with the monogluthathione conjugate. Systematic histopathology evaluations were limited to kidney and stomach, known target organs for chlorothalonil. Both test articles caused substantial kidney lesions. Standard H&E staining revealed epithelial hyperplasia and tubular

hypertrophy in the majority of rats in both treated groups, with karyomegaly in some chlorothalonil rats. Specialized staining was performed on additional kidney tissue samples by C.E.R.T.I. Laboratoire d'histopathologie, Versailles, France. C.E.R.T.I. evaluation showed vacuolar degeneration, tubular ectasis, tubular casts, interstitial fibrosis, and foci of basophilic tubules in both treatment groups, with the chlorothalonil group generally more affected. Only chlorothalonil caused lesions of the epithelium of the nonglandular stomach: hyperplasia, hyperkeratosis, erosions, and ulcers. Both test articles underwent further metabolism. A common trithiol metabolite was 3 to 5-fold more abundant in urine of the chlorothalonil group, suggesting that the monoglutathione conjugate was less available than chlorothalonil for further metabolism. Results indicated that glutathione conjugation was involved in kidney toxicity associated with chlorothalonil. "Acceptable ancillary study." No "adverse effects" indicated, except to characterize previously recognized effects. Aldous, 6/20/95.

275-138 054950 The same report as Record No. 133338, above. It had been submitted by 1987 and had received a brief review by B. Davis on 12/11/87.

SUBCHRONIC: MOUSE (SUPPLEMENTAL)

132, 108 050898-9, 034375 "A 90-Day Feeding Study in Mice with Technical Chlorothalonil" (Concord Woods Animal Facility, SDS Biotech Corporation, 9/2/83, Study No. 5TX-83-007). Technical Chlorothalonil (98.4% purity) fed to 15 mice/sex/group at 0, 7.5, 15, 50, 275, and 750 ppm for 13 weeks with an interim sacrifice of 5 mice/sex/group at 6 weeks. Possible adverse effects: increased alkaline phosphatase levels, elevated kidney weights, slight hyperplasia of renal epithelium, hyperplasia and hyperkeratosis of the gastric epithelium. NOEL = 15 ppm (2.5-3.0 mg/kg/day) for 13 weeks. Supplementary study. 050899 and 034375 are supplementary histopathology evaluations. Davis, 5/26/87. EPA ONE-LINER: NOEL = 15 ppm. LEL = 50 ppm - hyperplasia and hyperkeratosis of gastric mucosa. CORE GRADE Minimum

SUBCHRONIC: RABBIT (SUPPLEMENTAL)

138, 139 054951, 054952 "21-Day Repeated Dose Dermal Toxicity Study in Albino Rabbits With Technical Chlorothalonil," Sponsor Reference No. 5TX-85- 0023. (SDS Biotech Corporation, WIL Research Laboratories, Inc., Experimental Pathology Labs 4/11/86) Dermal application of chlorothalonil to 6 New Zealand White rabbits/sex/group at 0, 0.1, 2.5, or 50.0 mg/kg/day (dose volume of 1.0 ml/kg) for 21 days. No toxicity except dermal irritation accompanied by minimal to slight histopathologic changes. Urinalysis of 2 high dose animals showed no sulfur-containing metabolites. NOEL = 0.1 mg/kg/day. No adverse effect; Supplementary study. Davis 12/15/87.

CHRONIC TOXICITY, DOG

OVERALL "ADVERSE EFFECTS" EVALUATION: There are several dog studies ranging from 3 months to two years in duration. The 1995 Huntingdon Life Sciences study (Record # 153914) was the only study considered to have elicited a "possible adverse effect." This was based on an atypical response in one high dose female (mean dose for this group was about 354 mg/kg/day) and on stomach pathology at that dose level. The latter study involved dietary administration. An acceptable chronic study, completed in 1994 by Pharmaco LSR, used gelatin capsule administration of test article

shortly after feeding half of the daily ration. The balance of the daily ration was presented about 30 minutes after dosing. Although the high dose level in the latter study was 500 mg/kg/day, there was no remarkable stomach pathology, nor were there treatment-related deaths nor serious pathology. There were no adverse effects noted in the acceptable 90-day subchronic study (also capsule administration) which preceded the LSR chronic study. None of the other dog studies on file indicated adverse effects. Evidently the split-feeding capsule dosing methodology reduced the extent of stomach irritation to an insignificant extent. It is noteworthy that both the 1994 Pharmaco LSR study and the 1966 Hazleton 2-year dietary study involved higher dosage ranges than the 1995 Huntingdon study. Collectively, the data do not indicate chronic adverse effects in dogs. Aldous, 4/21/97.

****275-215 134264** Mizens, M. and Laveglia, J., "A chronic (12-month) oral toxicity study in dogs with technical chlorothalonil," Pharmaco LSR Inc., 12/19/94. Pharmaco LSR Study No. 92-3125. Chlorothalonil, purity 98.3%, was administered in gelatin capsules to 5 beagles/sex/group at 0, 15, 150 or 500 mg/kg/day for 12 months. No NOEL was found: plasma ALT levels were markedly reduced at all dose levels tested. There were no evident functional deficits nor liver microscopic lesions accompanying this change. The NOEL for other findings is 15 mg/kg/day, based on elevated relative liver weights and an enhancement over the normal extent of pigmentation of kidney tubular epithelial cells. At 500 mg/kg/day, body weights were slightly suppressed, and slightly elevated plasma cholesterol and slightly reduced circulating albumin suggested minor functional change in liver. Ophthalmology was negative. Study is acceptable, with no adverse effects. (Kishiyama and Aldous, 5/17/95).

****275-227 138982** Fillmore, G. E. and Laveglia, J., "A 90-day oral dosing study in dogs with chlorothalonil." Bio/dynamics (Study No. 92-3820), April 6, 1993. Four beagles/sex/group were dosed with 0, 15, 150, or 500 mg/kg/day chlorothalonil by gelatin capsule for 3 months. [The high dose was initiated at 750 mg/kg/day, but dose was reduced to 500 mg/kg/day on day 5 due to a death of a 750 mg/kg/day male on day 3. The death was attributed to test article, since there was associated emesis in all 750 mg/kg/day dogs, and no apparent food consumption in this particular dog on day 2. Necropsy of this dog was consistent with death due to aspiration of vomitus, which led to severe pulmonary edema, hemorrhage, necrotizing bronchitis, and diffuse pneumonia.] The adjusted (500 mg/kg/day) high dose was much better tolerated. Emesis was slightly elevated at that dose. This valid study does not indicate a "possible adverse effect." There is no absolute NOEL for this study, due to marked reductions of SGPT activity at all dose levels. Excluding this finding, the NOEL is 15 mg/kg/day, based on decreased body weight gain (males) and serum chemistry changes of decreased albumin levels (males), and increased cholesterol levels (females). These serum chemistry changes were observed in both sexes at 500 mg/kg/day, consistent with modest increases in relative liver weights. There were no direct treatment-related histopathological responses. Data support dose levels chosen for the chronic study of 0, 15, 150, and 500 mg/kg/day (see Record No. 134264). Aldous, 7/26/95.

275-177 118621 Interim report reviewed by Aldous, 9/19/94. Subsequently superseded by Record No. 138982, above).

275-177 118620 Commentary by G. Fillmore on 177:118621, above (no unique data, no DPR worksheet). Aldous, 9/19/94.

275-177 118622 "A 30-day oral toxicity study in dogs with T-117-12" (Final Report). Fillmore, G. E. and Laveglia, J., Bio/dynamics Study No. 91-3762. This study employed dose levels of 0, 50, 150, or 500 to 2/beagles/sex for 30 days. Findings were comparable to study 177:118621. In addition, histopathology was completed in this study, and was negative. No adverse effects indicated. No DPR worksheet. Aldous, 9/19/94.

****275-306 153914** Spencer-Briggs, D. J., "Chlorothalonil: Toxicity to dogs by repeated dietary administration for 52 weeks," Huntingdon Life Sciences, Ltd., HRC Project No. VCM/14, 12/21/95. Four beagles/sex/group were dosed in diet with 0, 160, 1280, or 10240 ppm chlorothalonil (99.28% purity) for 1 year. NOAEL = 160 ppm (stomach pathology; including prominent apoptotic bodies in the antrum, erosion of luminal surface epithelium, cellular hypertrophy with increased mucosal thickness, congestion of submucosal vessels, inflammatory cell infiltration in gastric mucosa, mucus and cell debris adherent to the luminal surface, and foci of mucosal mineralization). One high dose female was sacrificed moribund after displaying marked and sustained signs of anemia, reduced food consumption, and serious cardiac pathology. None of these signs were characteristic responses of other dogs at any dose level in the study. The above stomach pathology, and the anemia and heart pathology characterizing the atypical response of one dog, constitute a **"possible adverse effect."** No NOEL was demonstrated for the adaptive response of elevated non-protein thiol concentration in kidneys of females. Findings of limited toxicological importance and/or apparent adaptive responses included body weight decrements, clinical chemistry changes, liver weight increases, pigmentation of kidney cortical tubule epithelium, adrenal cortical hypertrophy in high dose males only, and vasodilation evident in gums and/or ears in high dose dogs (judged to be a local irritant response). Study was classified as unacceptable in the 1997, requesting stability data on treated diet. Data were provided in Record No. 157567, below. This chronic study is re-classified as acceptable. Aldous, 4/18/97 (upgraded 2/5/98).

****275-315 157567** Spencer-Briggs, D. J., K. W. Ashman, D. P. Buist, D. Crook, A. Anderson, I. S. Dawe, R. M. Read, C. Gopinath, L. F. Chasseaud, and M. Hall, [Study submitted to upgrade chronic dog study (DPR Record No. 153914)]. "Chlorothalonil toxicity to dogs by dietary administration for 13 weeks," Huntingdon Research Centre, 11/4/94, Laboratory Study # VCM 12/920413. Chlorothalonil (99.18%) was administered in diet to 4 beagles/sex/group at 0, 160, 1600, or 16000 ppm for 13 weeks. In addition to usual subchronic study measurements, this study measured urinary non-protein thiol and thioether concentrations, and non-protein thiol concentrations in liver and kidneys. There is no NOEL for reduced ALT levels. This finding has been reported in several other studies, and does not correspond to liver histopathology, even at the highest dose level. NOEL (other than for ALT) = 160 ppm (5.6 mg/kg/day). The most definitive treatment response at 1600 ppm is hypertrophy of the zona fasciculata of the adrenals in males (seen in both sexes at 16000 ppm). There was an apparent reduction in concentration of non-protein thiols in urine of males and females at 1600 to 16000 ppm, however data are equivocal. Additional findings at 16000 ppm included modest body

weight and food consumption decrements, an apparent increase in non-protein thiol concentration in liver and kidney tissue, decreased serum albumin, increased serum cholesterol, an equivocal increase in urinary protein in females, increased adrenal weight in males, and an increased width of the zona glomerulosa in females. Study is acceptable, with no adverse effects. The data on formulated diet stability suffice to upgrade the chronic dog study performed at the same laboratory (Record No. 153914). Aldous, 2/5/98.

132 050901 "Two-Year Dietary Administration - Dogs. Final Report." (Hazleton Laboratories, Inc., Project No. 200-149, 11/7/66). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 4 dogs/sex/group at 0, 0.15, 1.5, or 3.0 % by weight in the diet for 104 weeks. An interim kill of one dog/sex/group at one year with the remainder sacrificed to terminate the study at two years. Original CDFA review (6/2/87) considered this study to represent a "possible adverse effect," apparently based on reductions in body weight gain and upon elevated kidney and thyroid weights at all dosages. The study was re-examined on 10/4/89, and CDFA determined that (1) the data do not indicate a "possible adverse effect," (2) a provisional NOEL could be established by considering the major chronic dog studies together, and (3) a major non-reconcilable deficiency (considering the overall chronic study data base) was lack of acceptable ophthalmology. Organs which appeared to indicate treatment effects at 1.5% to 3% level in this study were kidney (primarily tubular degeneration observed: hypertrophy, dilatation; also epithelial vacuolation, pigmentation, and regenerative growth), liver (pigmentation of hepatocytes and macrophages, and an increase over the normal range of hepatocellular irregularities), thyroid (pigmentation), and stomach (gastritis). Re-examination of the data available on 10/11/91 (below) suggests that an upgrade is not possible. Incomplete. Unacceptable. A replacement dog study is required. Deficiencies originally noted by B. Davis included: no NOEL established; inadequate information on test material, test animals, and randomization; no feed analysis; insufficient serum chemistry; complete lack of ophthalmology or of microscopic examinations of eyes; inadequate tissue examination protocol for histopathology; missing data; and lack of data analysis. Davis, 6/2/87, Aldous, 10/4/89 and 10/11/91. EPA ONE-LINER: Systemic NOEL < 0.15% (LDT). Kidney and liver pigmentation. CORE GRADE = Not stated

275-172 096393, 096394, and 096395 Three records of human medical surveillance data and limited chlorothalonil exposure data, detailed separately, below. Data relate to the non-rodent chronic study data gap requirement. The most rigorous of existing animal chronic studies is the dog study, 275-132:050901. New data are sponsored by ISK Biotech Corp. (formerly Fermenta ASC Corporation). The major data for possible persistent effects on workers' eyes are in Record 096393. These data indicate that there were no treatment-related chronic effects on eyes of workers at a major chlorothalonil production facility (Greens Bayou Plant in Texas). None of the records provides adequate assessment of worker exposure to facilitate risk assessment. Data are not acceptable: not upgradeable. A repeat dog study will therefore be needed. A memorandum from M. O'Malley (Worker Health and Safety Branch of this Department) is appended to this review. Aldous, 10/11/91.

155 066795 Letter from N. H. Wilson to Fermenta Plant Protection Company addressing the issue of lack of ophthalmology in the 1966 dog study. Supplement to 050901. Gee, 1/24/89. (Discussed by CDFA in 1/30/89 rebuttal response).

039 941872 “104-Week Dietary Administration-Dogs. Daconil 2787 (Technical). Final Report.” (Hazleton Laboratories, Inc., Project No. 200-206, 5/6/70) (831) Chlorothalonil (purity not stated) at 0, 60 or 120 ppm in the diet for 2 years to 8 dogs/group/sex with a 1 year interim sacrifice of half of the dogs. No adverse effects reported. Incomplete. Unacceptable: cannot be upgraded. Dose levels too few and too low; histopathology limited (only 3 organs examined); test material and treated feed not characterized; limited data analysis. Christopher 3/14/85, Davis 6/15/87. (This study was considered in Aldous review of 10/4/89).

115 035817 (K. L. Stemmer, University of Cincinnati, 6/19/70) Letter and report evaluating chronic dog study (039:941872). Dr. Stemmer disagrees with the report conclusion that there were kidney tissue anomalies in high dose males. The CDFA reviewer did not analyze this submission since the study in question is unacceptable and cannot be upgraded. Apostolou, 12/6/85.

039 941898 “Statement and Evaluation of Kidney Histopathology of Daconil 2787 in Rats and Dogs by Dr. Klaus Stemmer, University of Cincinnati” (6/19/70). Reference to chronic dog study (039:941872). Stemmer concludes there is no nephrotoxicity in either study; presents experimental evidence for artifactual basis of anomalies in the rat study. Analysis of other rat studies shows histological kidney alterations at higher doses. NOEL < 500 ppm. In summary, it is not nephrotoxicity in rats at issue, but rather the dose level. CDFA agreed that there is no nephrotoxicity in the referenced dog study, but concluded positive evidence in the rat study. Davis 12/2/86. EPA ONE-LINER: Systemic NOEL = 60 ppm. Systemic LEL = 120 ppm (histopathological changes in kidneys). Levels tested = 0, 60 or 120 ppm. CORE GRADE = Not stated.

133 050902 “16-Week Dietary Feeding - Dogs. Final Report.” (Hazleton Laboratories, Inc., Project No. 200-200, 12/4/67). Chlorothalonil (purity unknown) fed to 4 dogs/sex/group at 0, 250, 500, or 750 ppm for 16 weeks. No adverse effect reported; NOEL > 750 ppm. Incomplete, unacceptable: Not an SB-950 study; Additional deficiencies include failure to establish a NOEL; lack of information on test material, test animals, and randomization; no feed analysis; insufficient serum chemistry, ophthalmology, and histopathology; and lack of data analysis. Davis, 6/3/87. EPA ONE-LINER: Systemic NOEL < 250 ppm (LDT). Increased PBI. CORE GRADE = Not stated

ONCOGENICITY, RAT

The data gap is filled by the IRDC study (volumes 100-104, record numbers 34366, 34367, 34348-34352, 34372). The finding of renal tubular adenomas and carcinomas in this study was confirmed by an unacceptable oncogenicity study done by Gulf South Research Institute. In addition, an ancillary study (Vol. 164) involving Fischer 344 rats confirmed the presence of kidney and forestomach tumors in males and females, and determined NOEL's for lesions in both organs. Kidney lesions in rats, including renal tubular tumors, are consistent with the results of mouse studies (see ONCOGENICITY: MOUSE below), although oncogenicity in mice was restricted to males and did not appear to be dose related. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88). Davis, 1/88, amended by Aldous, 10/4/89. See also comment under heading “CHRONIC, RAT” on page 2, and a

section below entitled “ONCOGENICITY, RAT, INTERPRETIVE INFORMATION” (Aldous, 8/21/97).

****100-104, 131 034366, 034367, 034348-034352, 034372, 050897** Wilson, N.H., J.C. Killeen, and J. A. Ignatoski, “A Tumorigenicity Study of Technical Chlorothalonil in Rats” (SDS Biotech Document No. 099-5TX-80-0234-008; (IRDC, 5/28/85). Chlorothalonil (purity 98.1%) given in the diet to achieve 0, 40, 80 or 175 mg/kg/day to 60 F-344 rats/group/sex for 27 months (males) or 30 months (females). Possible adverse effect indicated based principally on renal tubular adenomas and carcinomas, forestomach papillomas and squamous carcinomas, and a dose-related exacerbation of chronic progressive nephropathy. Complete; acceptable. 050897 is a histopathologic reevaluation. Apostolou 9/20/85; Davis 5/27/87. The data were re-examined by Aldous on 9/28/94 (see next paragraph).

275-100 to -104 034366 to 034367, 034348 to 034352, and 034372 and supplementary information in 275-131 050897. Primary report (beginning with Record No. 034366) was Wilson, N.H. et al., “A tumorigenicity study of technical chlorothalonil in rats,” SDS Biotech Corp., Painesville, OH, 5/28/85. Report as previously amended was already accepted. The original CDFA review, performed in 1985, was designed as a data survey rather than as a detailed analysis. This study is a pivotal one because it identifies tumor responses in the kidney and non-glandular stomach, so that an analysis of the principal oncogenic and other chronic findings is needed to support risk assessment. This review presents the primary findings of the 1985 study, then evaluates the data along with that of the subsequent study in a lower dose range (the 1989 Ricerca study; Record No. 074770). The combined data indicate “possible adverse effect,” based on tumors of renal tubular epithelium and of the non-glandular stomach mucosa, as well on the relatively low NOEL for chronic progressive nephropathy (based on Record No. 074770), which is 4 mg/kg/day in males and 2 mg/kg/day in females. The highest dose level used in each of the two studies (about 175 mg/kg/day) exceeded body weight and survival criteria for the MTD, however the major findings extended to lower dose levels. Aldous, 9/28/94.

164 074770 Wilson, N.H., and J.C. Killeen, “A tumorigenicity study of technical chlorothalonil in rats.” Ricerca, Inc. (study was subcontracted to other facilities), June 7, 1989. Dietary admixture of 0, 1.8, 3.8, 15.2, or 183 mg/kg/day chlorothalonil (mean values based on extractability of technical. from assayed diet) to Fischer 344 rats, 65 sex/group (of which 10/sex/group were designated for 1-yr interim sacrifice). Duration of principal phase was 99 wk (183 mg/kg/day males), 111 (all other males), or 125 (all females): termination times based on survival. The pathologist examining kidney slides was “blinded” as to treatment (p. 18). The expected “possible adverse effects” were observed (with 53 to 55/sex/group “at risk” in all cases): incidence of renal tubular adenomas/carcinomas for controls through increasing dosages in M = 1, 1, 1, 4, 23; in F = 0, 0, 0, 0, and 32. Tubular-epithelial hyperplasia in kidneys was elevated in incidence and degree at 3.8 mg/kg/day and above. This hyperplasia was confirmed present in every animal bearing tubular cell tumors, except for 4 cases in which autolysis and/or chronic nephropathy prevented a definitive diagnosis. The association was considered to be strong evidence that the hyperplasia is a preneoplastic lesion. Incidence of forestomach papillomas/carcinomas for controls through increasing dosages was 0, 0, 3, 2, 5 for males

and 1, 1, 2, 5, and 9 for females. These tumors were associated with hyperplasia, hyperkeratosis, or erosions or ulcers in the forestomach. NOEL = 2 mg/kg/day in both sexes, based on hyperplasia and hyperkeratosis of non-glandular stomach, and on modest increases in kidney tubular-epithelial hyperplasia (the latter most evident at 1-yr interim sacrifice). Ophthalmology examinations were performed late in the study, and were negative. These observations contribute significantly to the chronic rodent study data requirements. The co-existence of non-neoplastic lesions with tumors in respective tissues is consistent with the possibility that non-neoplastic lesions were part of a progression toward tumors; however the possibility of independent mechanisms cannot be excluded. C. Aldous, 10/4/89; minor editing changes without new worksheet by Aldous on 9/18/95.

275-264 143378 (exact duplicate of 275-164:074770, except that this copy lacks original prints of micrographs).

****275-307 153915** Spencer-Briggs, D. J., "Chlorothalonil: Potential tumorigenic effects in prolonged dietary administration to rats," Huntingdon Life Sciences, Ltd., 1/17/96, Laboratory Study # VCM 15. Fifty CrI:CD®(SD)BR rats/group were dosed with 0, 15, 60, 240, or 1200 ppm chlorothalonil in diet for 2 yr in the oncogenicity study. An additional 20/sex/group were dosed for 1 yr before interim kill. No NOEL was identified in this study. Epithelial hyperplasia and hyperkeratosis of the non-glandular forestomach were dose-related in both sexes over all dose levels. NOAEL = 60 ppm [**"possible adverse effect"** = squamous cell tumors (papilloma or carcinoma) in two 240 ppm females, one 1200 ppm female, and three 1200 ppm males]. Additional common findings in forestomach at 60 ppm and above included ulceration and submucosal fibrosis and inflammatory cell infiltration. Forestomach surface was often grossly "thickened," "roughened," and/or "white." The above tumors were likely to have resulted from chronic irritation of the non-glandular surface of the forestomach. Kidney weights were elevated in 240 ppm males and in high dose males and females. The only characteristic kidney microscopic lesion was chronic progressive glomerulonephrosis at elevated incidence or degree in high dose rats. Urinary protein was commonly elevated in high dose rats, possibly reflecting kidney dysfunction. Centrilobular hepatocyte hypertrophy was elevated in high dose rats. This is an **acceptable** oncogenicity study. Aldous, 4/18/97.

087 941883 "Bioassay of Chlorothalonil For Possible Carcinogenicity" (Gulf South Research Institute for the National Cancer Institute Carcinogenesis Testing Program, 1978) Chlorothalonil (98.50% and 98% purity for the two samples used) at 5,063 or 10,126 ppm in the diet (time-weighted averages) to 50 Osborne-Mendel rats/sex/group; 10 matched negative control rats/sex; Doses initially 20,000 & 10,000 first week of dosing, then lowered to 10,000 & 5,000 for remaining 79 weeks; Dosed for 80 weeks, observed for 110 weeks; Possible adverse effect; Oncogenicity NOEL < 5063 ppm (Neoplasms of renal tubular epithelium). Chronic toxicity NOEL < 5063 ppm (Weight loss, rough and discolored hair coats, bright-yellow urine, pale mucous membranes, ataxia, tachypnea, epistaxis, dermatitis, hematuria, hyperactivity, and vaginal bleeding). Incomplete. Unacceptable. Only two doses, doses lowered during the study, test material changed during dosing, dosing only 80 weeks, missing individual data, too few control animals. See also the important criticisms raised in 069 031892. Christopher, 3/14/85 and Davis, 12/4/86.

069 031892 Diamond Shamrock 2/14/80 "A Position Statement: The Carcinogenicity Assessment of Chlorothalonil (Daconil)" Doc. No. 280-5TX-79- 0133-001; Supplemental information to 087 941883; Critical review of rat oncogenicity study points out deficiencies in dose selection, reporting, analysis, and conclusion. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable. Davis, 12/5/86.

069 031893 Diamond Shamrock 5/4/81 "Concerns About The Reporting of Data From The 'Bioassay of Chlorothalonil For Possible Carcinogenicity' In Rats"; Document No. 280-5TX-81-0123-001; Supplemental information to 087 941883; Critical review of rat oncogenicity study points out problems with grouping renal neoplasms, with spontaneous neoplasm frequencies, and with the study pathologists' views. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable. Davis, 12/5/86.

069 028412 Kentron, Inc., Arlington, VA 5/12/82; "Environmental risk assessment of the use of chlorothalonil. Phase II: Hazard analysis." KTR 221-81. Supplemental information to 087 941883; Review of rat oncogenicity study criticizes negative controls, spontaneous frequency of renal neoplasms in this rat strain, unreported high frequency of nephritis, and choice of doses. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable. Davis, 12/8/86. EPA ONE-LINER: Neoplasms of the renal tubular epithelium in both males and females. CORE GRADE = Not stated

137 054947 "Report of the Status of A Tumorigenicity Study of Technical Chlorothalonil in Rats" (In-Life Phase: IRDC; Histopathology: Experimental Pathology Labs; Supervision: Ricerca, Inc., Sponsor no. 84-0103, 2/12/87) 56 week report for a supplementary study; no significant effects. Davis 12/9/87.

069 28409, 28410 "Summary of Data Report and Evaluation, Section 4" (IARC Expert Committee 7/21/82) Possible adverse effect-Third draft of IARC report states that chlorothalonil produced adenomas and adenocarcinomas in rat kidneys but no oncogenicity in mice. (No worksheet done. Davis 1/7/88)

ONCOGENICITY, RAT, INTERPRETIVE INFORMATION

275-311 154982 Wilkinson, C. F., and J. C. Killeen, "A mechanistic interpretation of the oncogenicity of chlorothalonil in rodents and an assessment of human relevance," *Regul. Pharmacol. Toxicol.* **24**, 69-84 (1996). The article addresses relevance to humans of forestomach and renal tumors seen in chlorothalonil-treated rodents. It is primarily a review of studies performed by the registrants, many of which are reported in Document Nos. 275-165 and 275-191 to -197. Rodent forestomach tumors were considered of limited relevance because humans lack forestomachs, and the squamous epithelium of the esophagus in humans is not exposed to dietary toxins for extended periods as is the rodent forestomach. Authors gave several reasons why rodent renal tumors are of limited relevance. Some haloalkenes had previously been shown to be metabolized by GSH conjugation, followed by a series of hydrolytic cleavages of the GSH moieties, eventually producing toxic thiols

through the action of β -lyase. Chlorothalonil also produces GSH addition and cleavage products, which can undergo β -lyase activation to toxic thiols. Studies have shown that di- and tri-thiols of chlorothalonil interfere with electron transfer from succinate to coenzyme Q in rat kidney cortical mitochondrial preparations. There was no such interference with mono- and di-GSH analogs of chlorothalonil. This disturbance in energy metabolism would be expected to lead to intracellular ion transport failure, decline in ATP levels, and altered cellular membrane permeability. Ultimately, tubular epithelial cells die, followed by compensatory proliferation, hyperplasia, and neoplasia. Rats have much higher renal activities of γ -GT and of β -lyase than do humans. Also, rats excrete much higher levels of chlorothalonil-derived thiols in urine than do other species such as dogs or monkeys. Thus it appears that humans are far less susceptible than rats to renal toxicity which is predisposing to tumor development. Other studies show that chlorothalonil residues bind primarily to proteins, but not DNA. This, coupled with the negative mutagenicity studies, suggests that chlorothalonil oncogenicity is a threshold effect. Thus data support the mediation of thiol formation in renal tumor development, but do not prove this association, because it is not proven that the renal tumors result directly and exclusively from action of di- and trithiol metabolites. A more convincing case for the "toxic thiol" hypothesis would entail a long-term study in rats with limited or absent capacity to produce di- and tri-thiols. As indicated in this article, such capacity limitations could be achieved by sustained use of inhibitors of γ -GT or of β -lyase, or alternatively by using rats genetically deficient in one of these enzymes. Aldous, 8/21/97.

275-251 143345 Wilkinson, C. F, "A mechanistic interpretation of the induction of rodent forestomach and renal tumors by chlorothalonil" (April, 1995). Rats and mice have demonstrated forestomach tumors, as well as renal proximal tubular tumors, in response to chlorothalonil. Chlorothalonil and its major metabolites are considered non-genotoxic, suggesting that the above tumors should have thresholds. Both forestomach and renal tumors are preceded by cytotoxicity and compensatory cell proliferation and hyperplasia, suggesting that tumors may arise from "fixation" of spontaneous mutagenic events, which would not otherwise become manifest. The two tumor types in rodents do not apply to humans because (1) humans lack a forestomach, and (2) the metabolic events leading to rodent renal tumors occur only at very low levels in humans. Thus, it is proposed that chlorothalonil be assigned "carcinogenicity" classification of "Group D" or, at worst, "Group C." Various international expert committees have reviewed chlorothalonil oncogenicity data, and have concluded that it is not genotoxic, and should be regulated on a NOEL - Safety Factor approach. (No SB-950 review is relevant, since this is not a "study." Aldous, 1/11/96).

ONCOGENICITY, MOUSE

The data gap is filled by the Bio/dynamics Inc. study (volumes 077-082, record numbers 941877-941882). The findings of renal tubular adenomas and carcinomas and forestomach neoplasms in this study are consistent with the findings of rat studies (see ONCOGENICITY: RAT above). See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88). Davis, 1/88.

**275-077 to -082 941877-941882 Wilson, N.H., J.C. Killeen, and J.A. Ignatoski, "A Chronic Dietary Study in Mice with Technical Chlorothalonil," Bio/dynamics Inc. Study No. 5TX-79-0102,

2/24/83. Chlorothalonil (purity at least 97.7%) was administered at 0, 750, 1500 or 3000 ppm in diet to 60 Charles River CD-1 mice/sex/group for 24 months. Two tumor types were associated with treatment: kidney tubular adenomas and/or carcinomas in males only (incidence of 0, 6, 4, and 4 in controls through increasing dosage groups), and squamous cell papillomas and/or carcinomas in forestomachs of males and females (incidence of 0, 2, 5, and 2 in males, and 0, 2, 6, and 5 in females for respective controls through increasing dosage groups). These are “possible adverse effects.” Both tumor types had associated lesions which may have been preneoplastic. All treated groups had a characteristic renal tubular hyperplasia, which was much more common and of higher severity in males, and which was absent in controls of either sex (see Record No. 050900). The majority of treated mice of either sex had hyperkeratosis and/or hyperplasia of the forestomach squamous mucosa, and the squamous cell tumors often arose from within these lesions. Dose-related incidences of esophageal hyperkeratosis were seen in both sexes at all dose levels. There were other treatment-related lesions of lesser importance in kidneys or nonglandular stomach, mainly at higher dose levels. Acceptable. Other relevant records are 050900 (kidney tissue reevaluation), 054948 (stomach tissue reevaluation), and 059034 and 058175 (ancillary low dose range study in males to establish NOEL's). Christopher, 3/15/85; Davis, 12/10/87; and Aldous, 9/27/95. EPA ONE-LINER: Oncogenic NOEL < 750 ppm (LDT) (renal neoplasms in males and evidence of hyperplasia and/or tumorigenesis in the squamous cell and epithelial layer of the esophagus and stomach in both sexes). Systemic NOEL < 750 ppm (LDT) (decreased ovary weight, hyperplastic bone marrow, hyperplasia of splenic red pulp in males, increased kidney weight with surface irregularities, pelvic dilation, cysts, nodules, masses, tubular degeneration). Levels tested by diet in CD-1 strain 0, 750, 1500, and 3000 ppm. CORE GRADE = Supplementary for chronic effects; no NOEL demonstrated. Guideline for oncogenic effects.

275-132 050900 Wilson, N.H., J.C. Killeen, and J.A. Ignatoski, “Histopathologic reevaluation of renal tissue from a mouse tumorigenicity study with chlorothalonil (5TX-79-0102),” March 7, 1986. Kidney slides from the 2/24/83 Bio/dynamics study (Record Nos. 941877-941822) were examined by a recognized specialist in renal pathology, William M. Busey. This report was examined by B. K. Davis in 1987, and was also incorporated into the 1995 review of the primary study (see above).

275-137 054948 Wilson, N.H. and J.C. Killeen, “Histopathologic reevaluation of stomach tissue from a mouse tumorigenicity study with technical chlorothalonil (5TX-79-0102),” 10/20/86. Stomach slides from the 2/24/83 Bio/dynamics study (Record Nos. 941877-941822) were re-examined by the primary study pathologist, W. Ray Brown. This report was examined by B.K. Davis in 1987, and was also incorporated into the 1995 review of the primary study (see above).

070 941871 Brief (6-page) version of Record No. 941877, above.

275-145 and -146 059034 and 058175 Wilson, N.H. and J.C. Killeen, “A Chronic Dietary Study in Mice with Technical Chlorothalonil.” (In-Life Phase: IRDC. Histopathology: Experimental Pathology Labs. Supervision: Ricerca, Inc., Sponsor no. 84-0077, 6/12/87). Study was performed to establish NOEL's for Record No. 941877. Only males were used, since they were the more sensitive sex for kidney lesions, and as sensitive as females for forestomach effects. Chlorothalonil (98%) was fed to

60 CD-1 males/group at 0, 10/15, 40, 175, and 750 ppm (equivalent to 0, 1.57, 4.50, 21.3, and 97.8 mg/kg/day after correction for extractability from diet). Ten per group were sacrificed at the end of the first year, the rest maintained for 2 yr. The low dose was increased from 10 ppm to 15 ppm at week 18 to ensure mean exposure of at least 1.5 mg/kg/day. Possible adverse effect: very low NOEL for hyperplasia and hyperkeratosis of the squamous mucosa of the forestomach (15 ppm), and possibly treatment-related squamous cell tumors of the forestomach (2, 0, 0, 1, and 4 affected in controls through increasing dosage groups, respectively). A conservative NOEL for renal tubular changes was 40 ppm, based on slight increase in tubular hyperplasia and karyomegaly at 175 ppm. Acceptable supplementary study. Davis 10/6/87, 12/9/87: Aldous, 9/27/95.

275-137 054946 Interim report for Record No. 059034, above.

****275-308 153916** Spencer-Briggs, D. J., "Chlorothalonil: Potential tumorigenic effects in prolonged dietary administration to mice," Huntingdon Life Sciences, Ltd., 12/20/95, Laboratory Study # VCM 16. Fifty Crl:CD-1® (ICR) BR mice/sex/group were dosed in diet with 0, 15, 60, 240, or 960 ppm chlorothalonil (99.28% purity) for 80 weeks. Report is **acceptable**. There is no NOEL for this study (epithelial hyperplasias, both in the forestomach and at the limiting ridge, were dose-related in incidence and degree at all dose levels in males). Findings noted at 15 ppm appear to be reversible, so that 15 ppm can be considered as a chronic NOAEL, based largely upon cystic glomerular atrophy in kidneys of males. Appearance of squamous cell papillomas in the non-glandular stomach is a "**possible adverse effect**." These benign tumors appear to result from chronic insult to the surface of the forestomach, causing non-neoplastic forestomach lesions at dose levels much lower than those eliciting tumors. Aldous, 4/18/97.

087 038930 "Bioassay of Chlorothalonil For Possible Carcinogenicity" Gulf South Research Institute (for the National Cancer Institute Carcinogenesis Testing Programs, 1978). Chlorothalonil (98% purity) at 2688 or 5375 ppm (time-weighted average dose) to male B6C3F1 hybrid mice (50/group); and at 3000 or 6000 ppm (time-weighted average dose) to female B6C3F1 hybrid mice (50/group); dosed 80 weeks, then observed for 11-12 weeks; no adverse effects indicated. Incomplete. Unacceptable; Only two doses, doses lowered during the study, missing individual data, too few control animals, high frequencies of spontaneous tumors. Christopher, 3/14/85 and Davis, 12/4/86. EPA ONE-LINER: Oncogenic potential negative. CORE GRADE = Not stated

070 025236 "Summary of DS-3701 Toxicology Studies: Mouse Study"; Document No. 098-5TX-78-0024-0010; Lab & Report Date not stated; 4-Hydroxy-2,5,6- trichloroisophthalonitrile (DS-3700, possible chlorothalonil metabolite) fed for two years at 375, 750, or 1500 ppm. No tumorigenicity. Two sentence summary. Incomplete. Unacceptable. Davis, 12/3/86.

REPRODUCTION, RAT

**** 275-169 095496** "A Two Generation Reproduction Study in Rats with Technical Chlorothalonil," (F. Lucas and G. Benz, Dept. of Toxicology and Animal Metabolism, Ricerca, Inc., Document # 1722-87-0121-TX-003, 11/9/90). Chlorothalonil, Lot # D-5840923, 98.1% purity, fed in the diet for 2 generations with 2 litters per generation at 0 (control), 500, 1500, and 3000 ppm with 35

Sprague-Dawley (CD-VAF) rats/sex/group. Treatment occurred continuously through both successive generations, beginning 10 and 14 weeks prior to mating for the F0 and F1 generation rats, respectively. Parental NOEL was not established; the following findings were dose-related down to 500 ppm: Kidney tubular epithelial hyperplasia and hypertrophy (both sexes); kidney clear cell hyperplasia and karyomegaly (no NOEL in males); forestomach hyperkeratosis and squamous epithelial hyperplasia (both sexes). Kidney lesions were typically much more severe in males. Modest, but statistically significant decrements in body weight gain were seen throughout the study in F0 and F1 parents. Reduced 21-day pup weights were indicated for the F1a, F1b, F2a, and F2b litters at 3000 ppm. Developmental NOEL (reduction of litter weight) = 1500 ppm. No adverse effects. Acceptable. (H. Green, T. Kellner and C. Aldous, 9/27/91).

275-166 086558 Wilson, N. H., et al., "Reproduction dose-rangefinding study in rats with technical Chlorothalonil." Ricerca, Inc., 5/18/89. Chlorothalonil, 98.1% purity, was administered in diets of CD rats, 15/sex/group, at dose levels of 0, 200, 375, 750, 1500, or 3000 ppm, for 10 weeks prior to mating, and continuously through mating, gestation, and lactation periods. This rangefinding study did not find adverse effects. Parental NOEL = 750 ppm, based on weight gain decrements in males only (not dose related). Enlarged kidneys were noted in 3000 ppm F0 adults only (in 5/15 males and in 1/15 females). Tissues were not examined microscopically, however kidney lesions have previously been observed in several chronic and subchronic rat studies, and thus kidney findings are presumed to be treatment effects. Reproductive NOEL = 1500 ppm (reduced body weights of pups after day 14 (statistically significant at day 21). Based on this study, the doses to be used in the subsequent 2-generation study will be 500, 1500, and 3000 ppm in diet. Acceptability status is not applicable, since this is a rangefinding study; however this study was performed consistent with guidelines. Doses selected for the definitive study are justifiable, considering this study and previous studies together. Aldous, 5/29/90.

075, 037 941886, 038929, 038844 "Three-Generation Reproduction-Rats. DAC- 2787. Final Report" Doc. No. 1000-5TX-67-0005-001; (Hazleton Labs., 2/2/67) Chlorothalonil (purity not given) dosed first 7 weeks, then a blend of chlorothalonil (93.6%) plus metabolites dosed for remainder of study; 0, 1500, 15000 or 30000 ppm to 10 males and 20 females/group; top 2 dose groups switched to 0 level dosing during days 3-14; both groups then switched to 5000 ppm, with dosing increased in steps to 20000 ppm for the high dose group until the P1 generation was terminated at week 20, and dosing increased in steps to 15000 ppm for the mid-dose group until the P1 generation was terminated in the 30th week; the 0, 1500, and 15000 ppm groups were continued through three generations. Chronic Toxicity: Decreased parental weight gain in all three generations; histological changes in kidney, esophagus, and stomach (histopathology data for this study found in Record # 38929); growth suppression of pups from birth to weaning shown to be a post-natal effect by cross nursing of control and test litters; Chronic toxicity NOEL < 1500 ppm; Incomplete. unacceptable-multiple dose level changes, dose levels too high, test material changed, test materials insufficiently characterized, only two dose levels after the P1 generation, too few animals, males rotated among females, limited histopathology. Christopher 3/15/85, Davis 6/19/87. EPA ONE-LINER: Reproductive LEL < 0.15% (LDT). Depressed pup weights, gastric and esophageal acanthosis in offspring. Maternal NOEL < 0.15%. Depressed body weight. CORE GRADE = Not stated

075, 037 038929, 038844, 038845 “Three-Generation Reproduction-Rats. DAC- 2787” (834); (Hazleton Labs., 4/5/67) Chlorothalonil (93.6%) plus metabolites at 0 or 5000 ppm in the diet to 10 males and 20 females per group; three generation study; Chronic Toxicity-decreased parental weight gain in all generations; kidney anomalies in P3 males; growth suppression of pups from birth to weaning shown to be a post-natal effect; NOEL < 5000 ppm; Incomplete, unacceptable-supplemental study with one dose level; deficiencies are too few body weights, no feed analysis, males rotated among females, incomplete pathology, too few animals; no histopathology data (the data in the appendix are for 075 941886). Christopher 3/15/85, Davis 6/19/87. EPA ONE-LINER: Reproductive NOEL < 0.5% (single dose tested). Decreased fetal weight. Maternal NOEL < 0.5%; body weight depression. CORE GRADE = Not stated

070 025240 “Summary of DS-3701 Toxicology Studies: Three-Generation Rat Reproduction Study” (Doc. No. 107-5TX-78-0023-002); Lab & report date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile, DS-3701 (chlorothalonil metabolite) at 0, 10, 60 and 125 ppm; Mean pup weights during lactation reduced in the 60 and 125 ppm groups for both litters of all generations; NOEL = 10 ppm. Supplemental study-brief summary of study with related compound. Davis 12/3/86.

070 025239 “Summary of DS-3701 Toxicology Studies: One-Generation Rat Reproduction Study.” Doc. No. 529-5TX-81-0193-002; Lab & report date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile, DS-3701 (chlorothalonil metabolite); 0, 10, 20, 30, 60 & 120 ppm; mean pup weights lower during lactation in the 60 & 120 ppm groups for both litters; Very brief summary. NOEL = 30 ppm. Supplemental study-brief summary of study with related compound. Davis 12/3/86.

TERATOGENICITY, RAT

**075 029668 “A Teratology Study In Rats With Technical Chlorothalonil” (Doc. No. 517-5TX-82-0011-003); Diamond Shamrock Corp. Life Science Toxicology and WIL Research Labs., Inc. 5/13/83; Chlorothalonil (98% purity) at 0, 25, 100 or 400 mg/kg/day to 25 pregnant females/group on days 6-15 of gestation; maternal toxicity (deaths, diarrhea, alopecia, decreased weight gain, and food consumption) at 400 mg/kg/day; Post-implantation loss due to early embryonic deaths ascribed to maternal toxicity; Maternal toxicity NOEL = 100 mg/kg/day; developmental NOEL > 400 mg/kg/day. Complete. Acceptable. Christopher, 3/25/85. EPA ONE-LINER: Teratogenic NOEL > 400 mg/kg/day (HDT), Fetotoxic NOEL > 400 mg/kg/day, Maternal NOEL = 100 mg/kg/day, Maternal LEL = 400 mg/kg/day (mortality, reduced body weight, increased resorptions and post implantation bases (sic). Levels tested by gavage in Sprague-Dawley strain-0, 25, 100 and 400 mg/kg/day; CORE GRADE = Guideline

TERATOGENICITY, RABBIT

** 157 072174 “A Teratology Study in Rabbits with Technical Chlorothalonil.” (Bio/dynamics Inc., NJ, 10/4/88, 1544-87-0060-TX-002). Chlorothalonil, technical, 98.1%, Lot D-5840923; given by oral gavage in 0.5% methyl aqueous cellulose at 0 (vehicle), 5, 10 or 20 mg/kg/day, days 7 through 19 of gestation, 20 does/group. Maternal NOEL = 10 mg/kg/day (marginal effect on body weight). Developmental effects NOEL = 10 mg/kg/day (marginal reduction in fetal weights at 20 mg/kg/day). Originally classified “unacceptable” because the data of the primary study alone did not clearly demonstrate that the dose of 20 mg/kg/day was an adequate high dose. Upgraded to acceptable on receipt of the pilot study (see below), which demonstrated that dosages substantially higher than 20 mg/kg/day could not have been tolerated. J. Gee, 1/13/89, C. Aldous, 5/9/89.

158 073489 (pilot study to 157:072174) “A teratology dose range-finding study in rabbits with technical Chlorothalonil.” Bio/dynamics, Inc., 9/27/88. Seven NZW rabbits/group dosed with 5, 15, 30, or 75 mg/kg/day chlorothalonil (purity 98.2%). Treatment days 7-19 of gestation. Vehicle = 0.5% methyl cellulose, aqueous suspension. Findings at 75 mg/kg/day: 3 deaths and 3 abortions, markedly decreased body weight and food consumption, reduced feces and/or soft stool in all 7 females. Findings at 30 mg/kg/day: 2/7 premature deliveries (possibly treatment-related, considering abortions at top dose and the low historical control incidence of premature deliveries), decreases in food consumption associated with modest decreases in dam body weights, and increased incidence of reduced feces and/or soft stool (5/7 females). This study supports selection of 20 mg/kg/day for the primary teratology study. C. Aldous, 5/9/89.

075 941887 “Reproduction Rabbits, DAC-2787, Final Report” (833) (Doc. No. 1000-5TX-66-0003-001 (Hazleton Lab., Falls Church, VA 9/30/66) Chlorothalonil (no purity stated) administered orally in gelatin capsules at 0, 180, or 375 mg/kg/day for days 8-9, changed to 0, 62.5, or 31.25 mg/kg/day respectively for days 10-16 ; 8 does/group; Animals sacrificed days 22-23 because of maternal toxicity; Insufficient information to assess adverse effects; Incomplete. Unacceptable; Too few animals, dosing started day 8 instead of 6, animals sacrificed day 22-23 instead of day 28, dosages drastically reduced because of maternal toxicity and high and low groups reversed, only two dose levels. J. Christopher, 3/25/85.

275-262 143369 Exact duplicate of 275-075:941887, above.

275-037 (No record #) 9/30/66 Cover sheet and page 5 of 075 941887.

075, 070, 133 941884, 038851, 050903 “Teratogenicity Study of Daconil in Rabbits” (Doc. No. 000-5TX-75-2077-001, Institute of Environmental Toxicology, 5/30/75). Chlorothalonil (99.3%) by gavage at 5 or 50 mg/kg/day for days 6-18 of gestation to 9 pregnant dams/group plus 8 negative control dams; Maternal toxicity (decreased food consumption and body weights, and increased abortions at 50 mg/kg) NOEL = 5 mg/kg/day; Developmental toxicity NOEL > 50 mg/kg/day. Incomplete. unacceptable; Can't be upgraded-only two dose levels, too few animals per group, no description of abortuses, corpora lutea not counted. 38851 is a one paragraph summary; 50903 presents individual data. Christopher 3/25/85; Davis 6/3/87. EPA ONE-LINER: Teratogenic NOEL >

50 mg/kg (HDT). Maternal NOEL = 5 mg/kg. Maternal LEL = 50 mg/kg (four spontaneous abortions). Fetotoxic NOEL = not established, additional information needed. Levels tested by gavage in Japanese White (Funabashi) strain-0, 5.0 and 50 mg/kg. CORE GRADE = Supplementary. Supply individual pup data; examination details of aborted embryos in the 50 mg/kg test group.

GENE MUTATION

Bacterial and somatic cell gene mutation assays on chlorothalonil and Ames assays on a number of metabolites and impurities of chlorothalonil are consistently negative. The data gap is filled and there is no adverse effect. B. Davis, 1/88.

** 073 941889 "Activity of DTX-77-0035 in the Salmonella/Microsomal Assay for Bacterial Mutagenicity" Document No. 000-5TX-77-0035-001. (Microbiological Associates, 6/29/77) Ames assay with strains TA98, TA100, TA1535, TA1537 & TA1538; Chlorothalonil (97.8%) at 0.33, 0.66, 1.0, 3.3 or 6.6 ug/plate with and without activation; No mutagenicity; Complete. Acceptable. Christopher 3/26/85.

037 941889 Contains several pages from 073 941889.

100 034458 No date; Summary of 073 941889.

EPA ONE-LINER: Negative for TA-1535; TA-100; TA-1537 and TA-1538 (his) status (sic) of ST DAC-2787 plated at 0.33, 0.66, 1, 3.3, 6.6 ug/plate. CORE GRADE = Not stated

073 038922 (formerly 941893-1) "Report on Mutagenic Testing With DAC 2787" Document No. 000-5TX-74-0013-001. (Brown Univ., 1/2/74) Host-mediated Ames assay with 8 strains (not guideline strains) of Salmonella typhimurium; Chlorothalonil (99+% purity) at 6.5 mg/kg/day by mouth to 10 male mice for 5 days; Bacteria injected into the peritoneal cavity and recovered 3 hours later; Summary with no data; Insufficient information to assess mutagenicity; Incomplete. unacceptable. Christopher 3/26/85.

100 034356 No date; Summary of 073 038922.

073 038924 (formerly 941888-2) "Mutagenicity Testing on Daconil in Microbial Systems" Document No. 000-5TX-61-0002-001. (Institute of Environmental Toxicology, Japan, No study date) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1538; Chlorothalonil (99.3% purity) at 0, 1, 2, 5, or 10 ug/plate without activation and 0, 2, or 10 ug/plate with activation; 2 plates/group; Insufficient information to assess mutagenicity; Incomplete. Unacceptable; no cytotoxicity observed with activation and hence no evidence that top dose was high enough, too few doses, too few replicates. Christopher 3/26/85.

073 038923 (formerly 942888-3) "Mutagenicity Testing on Daconil in Microbial Systems" Document No. 000-5TX-61-0002-001. (Institute of Environmental Toxicology, Japan, No study date) E. coli strains WP2 hcr+ and WP2 hcr-; Chlorothalonil (99.3% purity) at 0, 10, or 100 ug/plate (4

replicate plates/level) with activation and 0, 10, or 100 or 500 ug/plate (2 replicate plates/level) without activation; Insufficient information to assess mutagenicity; Incomplete. Unacceptable; no evidence of cytotoxicity at highest doses. Christopher 3/26/85.

037 038846 No date; 3 pages taken from 073 038924 & 073 038923.

110 034413 “Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Technical Chlorothalonil (SDS- 2787)” Document No. 694-5TX-84-0064-002. (Microbiological Associates, 12/25/84) Ames assay with Salmonella typhimurium strains, TA98, TA100, TA1535, TA1537, TA1538; Chlorothalonil (no purity stated) at 0.5 to 50 ug/plate (5 concentrations) with activation or at 0.16 to 16 ug/plate (5 concentrations); renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Incomplete. unacceptable; The only deficiencies are the lack of test material purity information and the lack of a repeat confirming experiment. Christopher 9/23/85.

110 034415 8/31/84 Appendix B: Contract Laboratory Report for 110:034413.

073 941890 “Activity of Chlorothalonil in an In Vitro Mammalian Cell Point Mutation Assay” Document No. 000-5TX-77-0034-001. (Microbiological Associates, 6/29/77) Somatic fibroblasts (Chinese hamster V79 and Mouse BALB/3T3) Chlorothalonil (97.3% purity) in two hour exposures at 0.3 ug/ml tested only without activation for V79 cells, at 0.3 ug/ml with activation for BALB/3T3 cells, and at 0.03 ug/ml without activation for BALB/3T3 cells; Insufficient information for mutagenicity assessment; Incomplete. unacceptable; too little information on methods of calculations, number of plates and cells; negative control frequencies too high for V79 cells; too few 3T3 cells to establish spontaneous mutation frequencies; too few dose levels; no confirmatory assay. Christopher 3/26/85.

100 034354, 034355 No date; One paragraph summary of 073 941890.

EPA ONE-LINER: Negative for Chinese hamster cells V-79 and BALB/3T3 mouse fibroblasts. Dose = 0.3 ug/ml for 2 hours. CORE GRADE = Not stated

037 027705 (formerly 941810) (Microbiological Associates, 6/29/77) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 & TA1538; 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3701), a metabolite of chlorothalonil, (99% pure) at 1, 3.3, 10, 33.3 or 100 ug/plate both with and without activation; Insufficient information to assess mutagenicity; Supplementary study. Christopher 3/15/85.

110 034414 “Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5,6-Tetrachloro-3-cyano- benzamide (SDS-19221)” Document No. 694-5TX-84-0087-002. (Microbiological Associates, 1/18/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5,6-tetrachloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at

10 to 1000 ug/plate (5 concentrations) with activation of 6.0 to 600 ug/plate (5 concentrations) without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034416 10/19/84 Appendix B: Contract Laboratory Report for 110:034414

110 034417 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-3-cyano-benzamide (47524)" Document No. 694-5TX-84-0088-002. (Microbiological Associates, 1/18/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-trichloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000 or 2000 ug/plate with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034418 11/15/84 Appendix B: Contract Laboratory Report for 110:034417.

110 034419 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-4-hydroxy-3- cyano-benzamide (SDS-47525)" Document No. 694-5TX-84-0089-002. (Microbiological Associates, 1/18/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-4-hydroxy-3- cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 40 to 6000 ug/plate (5 concentrations) with activation and 20 to 2000 ug/plate (5 concentrations) without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034420 10/19/84 Appendix B: Contract Laboratory Report for 110:034419.

110 034421 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,3,5,6-Tetrachlorobenzonitrile (SDS-3032)" Document No. 694-5TX-84-0091-002. (Microbiological Associates, 2/7/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,3,5,6-Tetrachlorobenzonitrile, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000 or 2000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034422 12/28/84 Appendix B: Contract Laboratory Report for 110:034421.

110 034423 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5,6-Tetrachlorodibenzamide (SDS-3133)" Document No. 694-5TX-84-0092-002. (Microbiological Associates, 2/7/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5,6-Tetrachlorodibenzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 2500, 5000 or 10000

ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034424 12/28/84 Appendix B: Contract Laboratory Report for 110:034423.

111 034425 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5-Trichloro-3-cyano-benzamide (SDS-47523)" Document No. 694-5TX-84-0093-002. (Microbiological Associates, 2/8/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5-Trichloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000, or 2000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034426 12/28/84 Appendix B: Contract Laboratory Report for 111:034425.

111 034427 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-4-thio- isophthalonitrile (SDS-13353)" Document No. 694-5TX-84-0124-002. (Microbiological Associates, 5/22/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-4-thio-isophthalonitrile, a potential metabolite of chlorothalonil, (purity > 90%) at 400, 630, 1000, 1600, 2500, 4000, or 5000 ug/plate with activation (plus additional levels of 2000 & 3000 ug/plate with TA100) and 250, 400, 630, 1000, 1600, or 2500 ug/plate without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034428 3/29/85 Appendix B: Contract Laboratory Report for 111:034427.

111 034429 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-3-carboxy- benzamide (SDS-46851)" Document No. 694-5TX-84-0139-002. (Microbiological Associates, 6/24/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-3-carboxy-benzamide, a potential metabolite of chlorothalonil, (99.4% purity) at 0, 100, 500, 2500, 5000, 10000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034430 3/28/85 Appendix B: Contract Laboratory Report for 111:034429.

111 034431 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5-Trichloroisophthalonitrile (SDS-5473)" Document No. 694-5TX-84-0086-002. (Microbiological Associates, 1/29/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5-Trichloroisophthalonitrile, an impurity and potential metabolite of chlorothalonil, (purity not stated) at 0, 0.5, 2.5, 10.0, 35.0, or 70.0

ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034432 10/19/84 Appendix B: Contact Laboratory Report for 111:034431.

111 034433 “Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,3,5,6- Tetrachloroterephthalonitrile (SDS-2020)” Document No. 694-5TX-84-0090-002. (Microbiological Associates, 1/15/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,3,5,6- Tetrachloroterephthalonitrile, an impurity and potential metabolite of chlorothalonil, (purity not stated) at 0, 4, 20, 100, 200 or 400 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034434 11/15/84 Appendix B: Contract Laboratory Report for 111:034433.

111 034435 “Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Isophthalonitrile (IPN) (SDS- 3176)” Document No. 694-5TX-84-0094-002. (Microbiological Associates, 2/19/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; Isophthalonitrile, an impurity of technical chlorothalonil, (purity not stated) at 0, 40, 200, 1000, 2000 or 4000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034436 12/28/84 Appendix B: Contract Laboratory Report for 111:034435.

111 034437 “Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Pentachlorobenzonitrile (SDS- 3297)” Document No. 694-5TX-84-0095-002. (Microbiological Associates, 2/14/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; Pentachlorobenzonitrile, an impurity of technical chlorothalonil, (purity not stated) at 0, 10, 50, 250, 500 or 1000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034438 12/28/84 Appendix B: Contract Laboratory Report for 111:034437.

133 050908 “Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,-Dichloro-4,6- bismercaptoisophthalonitrile (SDS-3939)” Study Number 5TX-85-0042. (Microbiological Associates, 10/22/85) This potential metabolite (90.5 + 2% purity) of chlorothalonil was tested at 50 to 4000 ug/plate (5 concentrations) without activation and 50 to 10,000 ug/plate (5 concentrations) with activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; renal activation system; triplicate plates; partial repeat assays; No adverse effect indicated; Supplementary study. Davis 6/8/87.

133 050909 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 5-(2,4-Dicyano-3,5,6- trichlorophenyl) Glutathione (SDS-66382)." Study Number 5TX-85-0043. (Microbiological Associates, 10/22/85) This potential metabolite (97.5 purity) of chlorothalonil was tested at 100, 500, 2500, 5000, and 10000 ug/plate with and without activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; renal activation system; triplicate plates; No adverse effect indicated; Supplementary study. Davis 6/9/87.

140 054954 "Salmonella/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With 5-Chloro-2,4,6- trismercaptopisophthalonitrile (SDS-66471)." Study Number 1097-86-0037. (Microbiological Associates, 12/19/86) This potential metabolite (96.2% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with no repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

140 054955 "Salmonella/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With S,S'-(2,4-Dicyano- 3,6-Dichlorophenyl)- Dicysteine (SDS-66474)." Study Number 1097-86-0038. (Microbiological Associates, 1/20/87) This potential metabolite (95% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with some repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

140 054956 "Salmonella/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With S,S',S''-(2,4- Dicyano-6-Chlorophenyl)- Tricysteine (SDS-66473)." Study Number 1097-86-0039. (Microbiological Associates, 12/19/86) This potential metabolite (> 95% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with no repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

037 027707 (formerly 941897-2) (Microbiological Associates, 6/29/77) Somatic Cell (Chinese Hamster V79 & mouse fibroblast BALB/3T3); 4-Hydroxy-2,5,6- trichloroisophthalonitrile (DS-3701), a chlorothalonil metabolite (99% purity) at 30 ug/ml + activation; Insufficient information to assess mutagenicity. Supplementary study. Christopher 3/15/85.

CHROMOSOMAL EFFECTS

Revised summary: A number of chromosome assays have been submitted, including in vivo studies in mice, rats and hamsters, somatic cell culture assays, and a barley seed assay. Of the 14 in vivo studies, none tests for mutagenicity in females, but this has been justified in the rebuttal of 11/24/86 based on the considerable evidence from other studies that males are more sensitive to chlorothalonil. The data gap is filled by seven acceptable studies. Among these acceptable studies, in vivo chromosome aberration assays in mice, rats, and (with one exception) hamsters were negative: one

acute hamster assay was marginally positive at high doses. An in vitro CHO chromosome aberration assay was positive (statistical significance only at the high dose) without activation. Thus there is some evidence for mutagenicity, which is mitigated by the following factors: 1) The in vitro assay was positive only without activation (This argument is weakened by the positive effect with and without activation in a brief NTP report-see Records 34361 and 34362), 2) The effect in the acute hamster study was marginal even at quite high doses (2500 and 5000 mg/kg), 3) metabolism studies suggest that only metabolites are absorbed through the rat gastrointestinal tract. In summary, the data gap is filled, and a possible adverse effect had previously been identified, with the caveat that the evidence is equivocal. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88). Two recent in vivo studies (acceptable) in rats and hamsters have been reviewed with no indication of chromosomal aberrations identified. The weight of evidence, therefore, is that chlorothalonil is not genotoxic, consistent with the results of the great majority of in vivo studies. Davis, 1/88, updated by Gee, 1/11/96.

073 941895 "The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day; oral gavage twice with 24 hour interval to 10 males/dose level (1 death following dosing); animals sacrificed 6 hours after second dose; Schmid protocol used; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 941895.

EPA ONE-LINER: No induction of Wistar strain rat bone marrow erythrocyte nuclei at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg. CORE GRADE = Acceptable.

073 038925 (formerly 941895-2) "The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 to 13 male mice/group; oral gavage twice with 24 hour interval; Schmid protocol used; mice sacrificed 6 hours after second dose; Insufficient information to assess adverse effects; Incomplete. unacceptable- Needs more sample times at longer intervals, Dose-independent mortality of 9/57 treated mice suggests technical problems. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 038925.

EPA ONE-LINER: Does not induce mouse bone marrow erythrocyte micronuclei in Swiss CFLP strain at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg. CORE GRADE = Acceptable.

073 038926 (formerly 941895-3) “The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil” Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83); Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 male hamsters/group (2 deaths following dosing); oral gavage twice with 24 hour interval; hamsters sacrificed 6 hours after second dose; Schmid protocol used; Insufficient information to assess adverse effects; Incomplete. unacceptable.-Needs more sample times at longer intervals. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 038926. EPA ONE-LINER: No significant increase in Chinese hamster bone marrow erythrocyte micronuclei at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg. CORE GRADE = Acceptable.

073 038919 (formerly 941893-2) (Brown University, 1/2/74) Mouse Micronucleus Assay; Chlorothalonil (99+% purity) at 6.5 mg/kg/day by mouth to 10 mice (sex & strain not specified) for 5 days; Sacrificed 3-4 hours post- dosing; Insufficient information to assess adverse effects; Incomplete. unacceptable; No rationale for protocol: only one dose, repeated doses with one sample time, sacrificed too soon; Too little information on test material, animals, procedures. Christopher 3/25/85.

073 941896 “The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil” Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France 1/2/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day to 10 to 11 male rats/group (1 death following dosing); oral gavage twice with 24 hour interval; rats sacrificed 6 hours after second dose and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

EPA ONE-LINER: Significant numbers of chromosomal abnormalities not induced in Wistar rats at up to 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg/day. CORE GRADE = Acceptable.

073 038927 (formerly 941896-2) “The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil” Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 to 11 male Swiss CFLP mice per group (3 dose- independent deaths following dosing); oral gavage twice with 24 hour interval; mice sacrificed 6 hours after second dose and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable.-Needs more sample times at longer intervals. Christopher 3/27/85.

EPA ONE-LINER: Bone Marrow chromosomal anomalies not increased at levels up to 2500 mg/kg (HDT) in Swiss CFLP strain. Positive control was urethan at 2000 mg/kg. CORE GRADE = Acceptable.

073 038928 (formerly 941896-3) “The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil” Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day to 10 to 13 male Chinese hamsters/group; oral gavage twice with 24 hour interval; hamsters sacrificed 6 hours after second dose

and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

070 25234 Brief summary of 073 941896, 073 38927 and 073 38928.

EPA ONE-LINER: Bone marrow chromosomal anomalies not increased at up to 1000 (sic)mg/kg (HDT) in Chinese hamster. Positive control was MMS at 65mg/kg. CORE GRADE = Acceptable.

**109, 133, 100, 034401-4, 034412, 050905, 034359 “In vivo Bone Marrow Chromosomal Aberration Assay in Mice with a Single Dose of Technical Chlorothalonil” (C.E.R.T.I., France 6/20/85) Chlorothalonil (98.2% purity) at 0, 250, 1250, or 2500 mg/kg by single dose oral gavage to 10 male mice/group; Mice sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; No adverse effect; Complete. acceptable. 34359 is a summary. Previously reviewed as unacceptable (J. Remsen (Gee) 9/23/85); additional data (133 50905) and rebuttal (11/24/86) make study acceptable. Davis 6/4/87.

**109, 133, 100 034405-8, 050904, 034358 “In vivo Bone Marrow Chromosomal Aberration Assay in Rats with a Single Dose of Technical Chlorothalonil” (C.E.R.T.I., France 3/18/85) Chlorothalonil (98.2% purity) at 0, 500, 2500 or 5000 mg/kg by single dose oral gavage to 10-14 male rats/group; Rats sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; Mitotic indexes of treatment groups unchanged from negative control value; No adverse effect. Complete, acceptable. 34358 is a summary. Previously reviewed as unacceptable (J. Remsen (Gee) 9/23/85); additional data (133 50904) and rebuttal (11/24/86) make the study acceptable. Davis 6/4/87.

**109, 133, 100 034409, 034410, 034412, 050906, 034360 “Acute In Vivo Bone Marrow Chromosomal Aberration Assay in Chinese Hamsters with T-117-11.” Study Number 5TX-83-0014. (C.E.R.T.I., France 6/17/85) Chlorothalonil (98.2% purity) at 0, 500, 2500, or 5000 mg/kg by single dose oral gavage to 10-13 male hamsters/group; Hamsters sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; 9 deaths in treated groups; dose- related decrease in mitotic index; Possible adverse effect-marginally increased aberration frequencies at 48 hours for 2500 and 5000 mg/kg; Statistically significant trend. Complete, acceptable. 34409 and 34412 are sponsor reports; 34360 is a summary. Previously reviewed as unacceptable (J. Remsen (Gee) 9/23/85); additional data (133 50906) and rebuttal (11/24/86) make study acceptable. Davis 6/5/87.

**109, 133, 100 034409, 034411, 034412, 050906, 034360 “Subchronic in Vivo Bone Marrow Chromosomal Aberration Assay in Chinese Hamsters with T-117-11.” Study Number 5TX-83-0014. (C.E.R.T.I., France 6/17/85) Chlorothalonil (98.2% purity) at 0, 50, 125, or 250 mg/kg/day for 5 days by single dose oral gavage to 10-11 male hamsters/group; Hamsters sacrificed 6 hours after the final dose and bone marrow cell chromosomes examined; 1 death/treated group; mitotic indices were elevated in all treated groups with statistical significance at 50 and 250 mg/kg/day; No adverse effect; Complete, acceptable. 34409 and 34412 are sponsor reports; 34360 is a summary. Previously reviewed as unacceptable (J. Remsen (Gee) 9/23/85); additional data (133 50906) and rebuttal (11/24/86) make the study acceptable. Davis 6/5/87.

**133 050910 “In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) Cells with Technical Chlorothalonil. Study Number 85-0082. (Microbiological Associates, 5/29/86) Chlorothalonil (98.8% purity) was tested at 0, 0.6, 1.5, 3.0, and 6.0 ug/ml with activation and 0, 0.03, 0.08, 0.15 and 0.30 ug/ml without activation; Numerical and structural aberrations scored; Possible adverse effect-increased structural aberrations without activation; Complete; acceptable; Davis 6/10/87.

100 034361, 034362 In vitro Aberrations and SCE's (Chinese hamster ovary cells), (National Toxicology. Program, 2/84) Chlorothalonil (no purity stated) positive for chromosome aberrations with and without activation and positive for sister chromatid exchange with activation; Incomplete. unacceptable: No dose levels stated; a one paragraph summary for the Annual Plan NTP-84-023. Apostolou 9/18/85.

073 941891 (formerly 941893-3) (Brown University, 1/16/74) Dominant Lethal Assay; Chlorothalonil (99+% purity) by gavage to 10 male mice for 5 days; Dosing stated to be : 1) 6.5 mg/kg/day on the Diamond Shamrock summary and page 8, 2) 6.7 mg/kg per day on page 3, and 3) three unspecified concentrations on page 2; Treated males mated to two different females each week for 8 weeks; Corpora lutea, total implantations, and dead implantations counted; Insufficient information to assess mutagenicity; Incomplete. unacceptable; Contradictory dose information leaves doses unknown; Too few pregnant females; No individual data; Too little information on animals used. Christopher 3/25/85.

100 034357 No date; Summary of 073 941891.
073 941894 (Tennessee State Univ., 1979) Chromosome Aberration Assay in Barley Seed; Chlorothalonil (75%) at 0, 250, 500 or 1000 ppm; 300 cells/group; Journal article; Incomplete. unacceptable; Not a guideline study; Too little information. Christopher 3/26/85.

070 941876 No date; Summary of micronucleus (941895, 38925, 38926) and chromosomal aberration (941896, 38927, 38928) tests in volume 073. See one- liners above.

** 275-257 143364 “Five-day repeated-dose chromosomal aberration test in vivo with SB-341 using rats.” (Y. Kajiwar et. al., Hita Research Laboratories, Chemical Biotesting Center, Japan, 9/7/94, study code K12-0001) SB-341 (chlorothalonil, 98.85%) was given by oral gavage to male rats [Crj:CD(SD)] on five consecutive days at 0 (olive oil), 500, 1000 or 2000 mg/kg. Five per dose were sacrificed at 6 and 24 hours after the last dosing. Mitomycin C was the positive control at 15 mg/kg with sacrifice at 18 hours. Two slides were prepared per animal and a total of 50 cells scored for aberrations. In a preliminary study, body weights were decreased at 500 mg/kg and above. No evidence of the induction of chromosomal aberrations following in vivo exposure of male rats was reported. Justification for using only males has been addressed in previous submissions. Acceptable. (Gee, 1/2/96)

** 275-258 143365 “In vivo bone marrow chromosomal analysis in Chinese hamsters following multiple dose administration of technical chlorothalonil.” (M. Mizens and J. Laveglia, Huntingdon

Research Centre, England, study number 94-0047, document number 6005-94-0047-TX-003, 6/2/95) Chlorothalonil technical (98.3%) was given by oral gavage to male Chinese hamsters at 0 (1% aqueous methylcellulose), 187.5, 375 or 750 mg/kg b. wt for 5 daily consecutive doses. There were 10 males per sacrifice time per dose. Cyclophosphamide was the positive control and gave the expected results. There were 4 mortalities at the high dose without the cause of death identified. Ten per group were sacrificed at 6 and at 24 hours after the final treatment for the vehicle and chlorothalonil groups; only 24 hours after a single dose for cyclophosphamide. Body weights were decreased at 375 and 750 mg/kg with some clinical signs, indicating the adequacy of the dose selection. No evidence of an increase in chromosomal aberrations due to treatment was reported. Use of only males was justified in earlier submissions. Acceptable. (Gee, 1/3/96)

DNA DAMAGE

Four studies with chlorothalonil and two with metabolites have been submitted in this category. Three of the chlorothalonil studies are acceptable. The acceptable Salmonella DNA repair assay shows a compelling positive result. The data from an unacceptable Bacillus subtilis study with the same test system also indicate mutagenicity though the study conclusions dismiss it. However, the other two acceptable studies (cell transformation and DNA binding) were both negative. The DNA binding assay is the most relevant study, since it was done in vivo and in a mammal (the rat) and organ (the kidney) which has been shown to be a target for both chronic toxicity and oncogenicity. Other studies have shed considerable light on the metabolism of chlorothalonil in mammals and it seems unlikely that bacterial systems would approach the same biochemistry, even in the presence of mammalian activating enzymes. Therefore, we consider there to be no adverse effect in this category. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88). Davis, 1/88.

**073 941897 “Activity of Chlorothalonil in a Test for Differential Inhibition of Repair Deficient and Repair Competent Strains of Salmonella typhimurium: Repair Test” Document No. 000-5TX-77-0033-001 (Microbiological Associates, 6/29/77) Chlorothalonil (97.8% purity) at 0, 2, 10 or 20 ug/plate + activation to matched S. typhimurium strains TA1978 (repair competent) and TA1538 (repair deficient) in a disc diffusion assay with agar overlay; Possible adverse effect; Three independent assays produced significant differences in growth inhibition between the strains at all dose levels of chlorothalonil with and without activation, suggesting DNA damage; NOEL < 2 ug/plate; Complete; acceptable. Christopher 3/25/85.

100 034363 No date; Summary of 073 941897. EPA ONE-LINER: Interferes with DNA repair in TA-1538. Tested at 2-20 ug/plate. CORE GRADE = Not stated

073, 037, 100 941888, 027708, 034364 “Mutagenicity Testing on Daconil in Microbial Systems” Document No. 000-5TX-61-0002-001 (Institute of Environmental Toxicology, Japan, 10/19/77) Chlorothalonil (99.3% purity) at 0, 2, 5, 10, 20, 100 or 200 ug/plate to matched Bacillus subtilis strains H17 (repair competent) and M45 (repair deficient) in a disc diffusion streak assay; Possible adverse effect-greater inhibition in M45 in treated plates; Incomplete. unacceptable: no activation; only one plate per dose level; no data analysis. 27708 and 34364 contain excerpts. Christopher

3/26/85, Davis 6/15/87. EPA ONE-LINER: Negative for DNA repair synthesis in *B. subtilis* #M44 (sic). CORE GRADE = Not stated

**073, 037 941892, 028258 “Cell Transformation Assay with Chlorothalonil” Document No. 041-5TX-79-0021-004 (Microbiological Associates, 1/14/80) Chlorothalonil (96% purity) at 0.001, 0.0001, or 0.00001 ug/ml of medium, incubated for 7 days with two rat cell lines (F1706 P95 & H4536 P+2 [infected with RLV]); each culture subcultured 12 times and assayed for foci after two weeks; subcultures 3, 6, 10, and 12 screened for ability to form macroscopic colonies in semisolid agar; high dose subculture 9 tested for ability to form tumors in newborn Fischer rats; No adverse effect; Complete, acceptable. 28258 contains pages ii and 4 of the report. Christopher 3/26/85, Davis 6/15/87.

EPA ONE-LINER: Negative for phenotypic transformations in F1706 and H4536p+2 cell lines. CORE GRADE = Not stated

**146 059035 “Determination of the Covalent Binding of Radiolabel to DNA in the Kidneys of Male Rats Administered C-Chlorothalonil (C-SDS-2787)” (Microbiological Associates, Inc., 7/9/87) Mixture of nonlabelled analytical grade chlorothalonil (98.9% purity) and C-labeled chlorothalonil (radiochemical purity of 99%) by gavage to 4 male rats with appropriate negative and positive controls; sacrificed after 6 hours; protein and DNA extracted from kidney tissue and analyzed by LSC; radiolabel was bound to protein but not DNA of kidneys from chlorothalonil-treated rats; No adverse effect; acceptable; Davis 10/14/87.

037 027706 (formerly 941897-1) (Microbiological Associates, 6/29/77) 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3700, a chlorothalonil metabolite, 99% purity) at 0, 2, 10 or 20 ug/plate + activation to matched *S. typhimurium* strains TA1978 (repair competent) and TA1538 (repair deficient) in a disc diffusion DNA damage assay with agar overlay; Insufficient information to assess mutagenicity: no data are included; Supplementary study; This report consists of a few pages from a full study. Davis 12/17/86.

070 025238 Document No. 041-5TX-80-0015-003; Lab & Report Date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3700, chlorothalonil metabolite) in a cell transformation assay with F1705 and H4536 cells; no in vitro transformation; treated cells injected into newborn Fischer rats; No tumors observed from H4536 cells; Late tumors observed in rats injected with F1705 considered to be spontaneous transformation, characteristic of this cell line; Very brief summary of a supplementary study. Davis 12/3/86.

METABOLISM STUDIES

275-165 086554 Savides, M. C., J. P. Marciniszyn, and Killeen, J. C., “Study to evaluate the urinary metabolites of Chlorothalonil from male Rhesus monkeys.” Animal Metabolism Laboratory, Ricerca, Inc., 4/16/90. (In-life phase of study was conducted at White Sands Research Institute, Alamogordo, NM). Four male monkeys were administered 50 mg/kg Chlorothalonil (analytical grade, 98.8%), to which was added ¹⁴C- chlorothalonil (uniformly labeled in the benzene ring, 142.5 mCi/mmol specific activity). A single oral dosing was done using 0.75% methylcellulose aqueous suspension.

Urine and feces were collected over four days. Urine samples were assayed for thiol content following derivatization with diazomethane. Half-life in blood was variable, ranging from 7 to 35 hr. From 2 to 4% of dose was excreted in urine: this compared to 52 to 92% which was excreted in feces, during the collection period of 4 days. Methyl-derivatized thiol metabolites were quantitated in urine: assays were capable of measuring monomethylthio-isophthalonitrile, as well as bis(methylthio) and tris(methylthio) derivative metabolites. Only the latter two could be detected, and the tri-thiol was the most abundant. Nevertheless, only about 0.001 to 0.01% of administered dose was recovered as tri-thiol and di-thiol isophthalonitriles, suggesting that this was a very minor pathway in monkeys. Aldous, 6/5/90.

275-165 086555 Savides, M. C., J. P. Marciniszyn, and Killeen, J. C., "Study of the urinary excretion of radio label by catheterized dogs following oral administration of 14C-Chlorothalonil by gavage." Animal Metabolism Laboratory, Ricerca, Inc., 4/17/90. Three male beagles were administered nominal doses of 50 mg/kg 14C-Chlorothalonil in single gavage administrations. Urine was collected for up to 24 hr by catheters (inserted into the bladders) to eliminate contamination by feces. Urine and feces were collected for a subsequent period (total of 8 days) with catheters removed. Total urinary excretion was estimated to be 0.7 to 1.9% of estimated actual dose: most of this was collected during the first 24 hr. Fecal elimination was estimated to be 83 to 99% of estimated actual dose. Analyses of urine for mono-, di-, and tri-thiols did not detect any of these metabolites. Aldous, 6/5/90.

275-165 086556 Magee, T. A., M.C. Savides, J. P. Marciniszyn, and Killeen, J. C., "Study to evaluate the metabolic pathway of Chlorothalonil (14C-ASC-2787) in germ-free rats." Ricerca, Inc., Department of Toxicology and Animal Metabolism, 4/18/90. "Germ-free" (lacking in intestinal flora) CD Sprague-Dawley male rats from U. Wisconsin Medical School, Madison, were dosed with 0.75% methylcellulose vehicle by gavage (single dose, 50 mg/kg Chlorothalonil). Daily urine samples were extracted for evaluation of thiol content (see methods in dog and monkey studies, this volume). Three of 9 rats had measurable levels of di- and/or tri- thiols from the 24 hr or 48 hr urine collection. Investigators noted that urine of non germ-free rats contains more than 50-fold more of these thiols as urine of germ-free rats evaluated in this study. Thus intestinal microflora are presumed to be responsible for the metabolites which are associated with kidney toxicity in non germ-free rats. This was stated to be particularly important, because the "The population of microflora in the upper gastrointestinal tract of man is much less than that in the non germ-free rat" (p. 36). Aldous, 6/5/90.

275-165 086557 Detailed report on in-life phase of 275-165:086556, above.

275-191 133333 Barrowman, J.A. (Study Director), "Recirculation of radioactivity in rat bile following intraduodenal administration of bile containing 14C-Chlorothalonil label," Memorial University of Newfoundland, SDS Biotech Study No. 4AM-79-0004. Uniformly-labeled chlorothalonil was administered into the duodena of Sprague-Dawley rats. Bile was collected via cannula. About 1 to 6% of administered label was excreted in bile. Bile collected during the first 6 hr after dosing was administered to recipient rats. About 19% of this label was excreted by the recipient rats within 24 hr. This suggests significant enterohepatic recirculation. Aldous, no worksheet, 6/20/95.

275-192 133334 Pollock, G.A., "Levels of radioactivity in blood following oral administration of ¹⁴C-Chlorothalonil (14C-DS-2787) to male rats," SDS Biotech Corp., 8/22/83. Principal finding was that very high dose levels led to delays in peak blood concentrations (5-6 hr for dose level of 5 mg/kg, 9 hr for 50 mg/kg, and about 16 hr for 200 mg/kg). Aldous, 6/21/95, no worksheet.

275-193 133337 Savides, M.C., "Pilot study for the determination of the effects of probenecid pretreatment on urinary metabolites and excretion of ¹⁴C-SDS-2787 following oral administration to male Sprague-Dawley rats," SDS Biotech Corp., 12/20/85. Probenecid is widely used to competitively inhibit active secretion of anionic metabolites from the proximal tubules of the kidney. In this study, probenecid led to (1) reduced urinary excretion of radiolabel, (2) increase in plasma radiolabel, and (3) reduction of kidney radiolabel. The first two observations were consistent with inhibition of the anionic transport system. It is not clear why there should be a reduction in radiolabel in kidney, since one would expect net accumulation of labeled anionic metabolites in the kidney. Aldous, 6/21/95, no worksheet.

275-195 133339 Savides, M.C., J. P. Marciniszyn, and Killeen, J. C., "Pilot study of the effect of the gamma-glutamyl transpeptidase inhibitor, AT-125, on the metabolism of ¹⁴C-Chlorothalonil," Ricerca, Inc., Painesville, OH, 3/15/88. AT-125 would be expected to inhibit metabolism of glutathione conjugates of chlorothalonil, so that one would expect reduced overall excretion of acidified urine samples into ethyl acetate, and far less excretion of thiol metabolites. Some SD rats were pretreated with AT-125, then all received 50 mg/kg chlorothalonil by gavage. Urine was collected at 6, 12, and 24 hr post dosing, then acidified to pH 2, and extracted with ethyl acetate. During the first 12 hr, the AT-125-pretreated rats excreted only about 15% extractable label, compared to about 75% in non-pretreated rats. Total excretion of radiolabel was not changed by AT-125 treatment. The major non-extractable components were evidently di- and triglutathione metabolites of chlorothalonil. Extractable components were not identified. Aldous, 6/21/95, no worksheet.

275-196 133340 Savides, M.C., J. P. Marciniszyn, and Killeen, J. C., "A study to evaluate the effects of sulfur-containing analogs of chlorothalonil on mitochondrial function," Ricerca Animal Metabolism Laboratory, 2/29/88. Rat liver or kidney mitochondrial preparations were incubated with ADP in a medium which would allow respiration to take place, with consumption of oxygen. Oxygen consumption was assayed in the presence and absence of chlorothalonil analogs (mono- and dithiol analogs, and mono- and di-glutathione analogs). Remarkable inhibition of mitochondrial respiration occurred primarily with the dithiol analog, and to a lesser extent with the monothiol analog. This implicates these products (particularly the dithiol in this study) as causative agents of kidney toxicity by disturbing mitochondrial respiration. Aldous, 6/20/95, no worksheet.

275-197 133342 Andre, J. C., J. P. Marciniszyn, and Killeen, J. C., "Evaluation of mitochondrial function in the presence and absence of sulfur-containing analogs of chlorothalonil," Ricerca, Inc., Painesville, OH, May 10, 1991. Project ID 88-0107. Kidney cortical mitochondrial preparations were made from CD* rats. Effects on respiration were studied in presence of chlorothalonil analogs (mono-, di-, and tri-thiol analogs, and mono-, di-, and tri-glutathione analogs). Each analog was tested in the presence of either succinate or glutamate (to identify, if possible, the stage of oxidative

respiration which might be affected). Both di-, and tri-thiol analogs inhibited respiration (measured by effects on oxygen consumption) in the presence of succinate, but not glutamate. Investigators concluded that these analogs inhibited mitochondrial respiration at the level of electron transfer from succinate to Coenzyme Q. This was proposed as a possible basis of nephrotoxicity of chlorothalonil, which forms glutathione metabolites and subsequently corresponding thiol metabolites, which are found in rat urine. Aldous, 6/20/95, no worksheet.

275-316 159183 Rosner, E., C. Klos, and W. Dekant, "Biotransformation of the fungicide chlorothalonil by glutathione conjugation," Dept. of Toxicology, University of Würzburg, Germany, *in Fundam. Appl. Toxicol.* **33**, 229-234 (1996). When chlorothalonil was incubated in rat liver cytosol in the presence of GSH, 4,6-bis(glutathion-*S*-yl)-2,5-dichloroisophthalonitril was the primary product. Using very brief incubation time (30 seconds), some 4-(glutathion-*S*-yl)-2,5, 6-trichloroisophthalonitril was detected [a presumed intermediate]. Male SD rats were administered acivicin (to inhibit γ -glutamyltranspeptidase) and had bile ducts cannulated prior to administration of single oral doses of 0.66 or 2.64 mmol/kg chlorothalonil. Bile was analyzed for chlorothalonil and metabolites. The only biliary product reported was a small amount of 4,6-bis(glutathion-*S*-yl)-2,5-dichloroisophthalonitril (chlorothalonil was not detected). Other male and female SD rats were dosed with chlorothalonil for urinary metabolite evaluation (presumably without acivicin pre-treatment. The only identified product was 4,6-bis(*N*-acetylcystein-*S*-yl)-2,5-dichloroisophthalonitril, which was found in only minor amounts, with no sex difference in amount detected. The major part of orally administered chlorothalonil was excreted in feces unchanged in all *in vivo* studies. Evidently the only other metabolite assayed was 4-(*N*-acetylcystein-*S*-yl)-2,5-trichloroisophthalonitril, hence there is no report of possible mono- di- or tri-thiol compounds in excreta. The study does not address any standard data requirements, but provides some useful data. Methods and results are too sparsely reported for a more thorough evaluation. Aldous, 2/17/98.

275-253 143353 Savides, M. C. *et al.*, "Study to determine the extent and nature of biliary excretion of chlorothalonil and/or metabolites in the dog. Part I." Ricerca, Inc., 4/10/95. Document No. 5521-93-0319-AM-001, Project ID 93-0319. [No DPR worksheet: the following is mainly from the report abstract]. Four male beagles had bile ducts cannulated one day before receiving a single oral dose of 50 mg/kg [14 C]-chlorothalonil by gavage (0.75% CMC suspension, 2.5 ml/kg body weight). Bile was collected hourly for 48 hr. Urine and feces were also collected. About 5.1% of administered dose was collected in bile, with peak excretion at 10-14 hr post -dosing. On average, 1.4% of administered dose was collected in urine. Total absorbed dose (all routes) was calculated to average 7.7% of administered dose. Bile sample label was highly polar (only 2% was extractable into diethyl ether). Preliminary evaluation of cationic fraction of bile residues revealed a complex pattern of constituents. Urinary sample extracts were also complex, however "No radioactivity was present at HPLC retention times corresponding to dithiol, trithiol, or mono, di, and tri-*S*-methyl derivatives of chlorothalonil." Aldous, 2/2/98.

275-254 143354 Magee, T. A. *et al.*, "Study of the urinary excretion of radiolabel by dogs following administration of [14 C]-chlorothalonil by gavage." Ricerca, Inc., 12/6/91. Document No. 3086-90-0229-AM-001, Project ID 90-0229. [No DPR worksheet: the following is from the report abstract]. Three male beagles were administered a single oral dose of 50 mg/kg [14 C]-chlorothalonil by gavage

(0.75% CMC suspension). Urine was collected at 2 hr intervals for the first 24 hr. Feces were collected after each defecation for 24 hr. Subsequently, urine and feces were collected at 24-hr intervals for a total of 72 hr. Recovery of label was 95.3% (1.4% in urine and 93.8% in feces). Urinary residues were evaluated. No mono- or di- (methylthio) metabolites were found. One sample contained 0.00012% of administered dose as tri- (methylthio) metabolite. This was noted to be a very low yield of thiol metabolites compared to that of rats. Aldous, 2/2/98.

275-255 143355 Magee, T. A. *et al.*, "Study in dogs to evaluate the pharmacokinetics of [¹⁴C]-chlorothalonil. Ricerca, Inc., 6/18/92. Document No. 3421-89-0325-AM-001, Project ID 89-0325. [No DPR worksheet: the following is from the report abstract]. Four male beagles were administered a single oral dose of 50 mg/kg [¹⁴C]-chlorothalonil by gavage (0.75% CMC suspension). One dog was sacrificed at each of the following intervals (2, 9, 24, and 96 hr). Urine, feces, and blood were collected at intervals, and selected tissues were collected at termination. Most label was present in feces and intestinal contents. Urine contained < 1% of radiolabel. Gallbladder contained the highest tissue level of radiolabel, followed by kidney. Only about 1% of label was still present in stomach and small intestine by 9 hr, indicating comparatively rapid passage. Thiols and similarly reactive moieties in extracts were methylated with diazomethane. In urine, there were no mono-(methylthio) residues. Six samples contained di-(methylthio) residues, and 13 samples contained tri-(methylthio) residues (about 1×10^{-5} and 1×10^{-4} % of administered dose, respectively. This was noted to be a very low yield of thiol metabolites compared to that of rats. Investigators considered results to account for the comparatively lower kidney toxicity of chlorothalonil in dogs compared to rats. Aldous, 2/2/98.

275-276 146573 "Study to evaluate the urinary metabolites of chlorothalonil following dermal application to male rhesus monkeys." This document is under review by Worker Health and Safety Branch as of 2/5/98 (Aldous).

METABOLITES

** 275-0420; 212548; "A Two-Generation Reproduction Study in Rats with SDS-46851"; (F. Lucas, J. Laveglia; Department of Toxicology & Animal Metabolism, Ricera, Inc., Painesville, OH; doc. no. 3822-91-0014-TX-004; 9/3/93); Thirty five Sprague Dawley rats/sex/group in the F0 generation received 0, 2000, 6000 or 20000 ppm of SDS-46851 (3-carboxy-2,5,6-trichlorobenzamide) (lot no. 0207; purity: 99.3%) in the diet for 10 weeks prior to mating and during mating for F1a (up to 2 weeks), 3 weeks each of gestation and lactation, at least one week prior to mating, mating for F1b (up to 2 weeks) and 3 weeks each of gestation and lactation. Thirty five animals/sex/group of the F1a generation were selected and received the test material in the diet at the same dose levels for 12 weeks prior to mating and during mating for F2a (up to 2 weeks), 3 weeks each of gestation and lactation, at least one week prior to mating, mating for F2b (up to 2 weeks), and 3 weeks each of gestation and lactation. There were no treatment-related effects upon the adults in either the F0 or F1 generations. There were no treatment-related effects upon any of the reproductive or developmental parameters for the F1 or F2 generations. **No adverse effect indicated. Parental NOEL:** (M/F) 20000 ppm ((M): 911 to 2621 mg/kg/day, (F): 1246 to 2669 mg/kg/day), **Reproduction NOEL:** (M/F) 20000 ppm ((M): 911 to 2621 mg/kg/day, (F): 1246 to 2669 mg/kg/day), **Developmental NOEL:** (M/F) (M/F) 20000 ppm (((M): 911 to 2621 mg/kg/day, (F): 1246 to 2669 mg/kg/day). **Study acceptable.** (Moore, 4/4/06)

** 275-0421; 212549; "An Oncogenicity Study in Mice with SDS-46851"; (F. Lucas, J. Laveglia; Department of Toxicology & Animal Metabolism, Ricera, Inc., Painesville, OH; Project No. 3584-91-0071-TX-003; 3/10/94); Sixty CD-1 mice/sex/group received 0, 1000, 3500 or 7000 ppm of SDS-46851-0207 (3-carboxy-2,5,6-trichlorobenzamide) (lot no. 0207, purity: 99.3%) in the diet for 18 months ((M) 0, 156.4, 542.2, 1116 mg/kg/day, (F) 0, 188.9, 649.4, 1308 mg/kg/day). Survival of the animals was not affected by the treatment. There was no treatment-related effect upon the mean body weights or food consumption. The differential leucocyte count did not reveal any treatment-related effects after either 52 or 77 weeks of treatment. In the necropsy examination, the mean organ weights were not affected by the treatment. The histopathological examination did not reveal any treatment-related non-neoplastic or neoplastic lesions. **No adverse effect indicated. Chronic Dietary NOEL:** (M/F) 7000 ppm ((M) 1116 mg/kg/day, (F) 1308 mg/kg/day); **oncogenicity is not evident. Study acceptable.** (Moore, 4/5/06)

** 275-0422; 212550; "A Combined Chronic Toxicity/Oncogenicity Study in Rats with 3-Carbamyl-2,4,5-Trichlorobenzoic Acid (SDS-46851)"; (J.C. Killeen, Jr., J. Laveglia, D.M. Serrone; Department of Toxicology & Animal Metabolism, Ricera, Inc., Painesville, OH; Doc. No. 3533-90-0030-TX-005; 11/23/93); Sixty Sprague-Dawley rats/sex/group received 0, 80, 200, 500 or 1000 mg/kg/day of SDS-46851-0207 (3-carboxy-2,5,6-trichlorobenzamide) (lot no. 0207, purity: 99.3%) in the diet for 24 months. Survival of the animals was not affected by the treatment. There was no treatment-related effect upon the mean body weights or food consumption. The hematology and clinical chemistry evaluations and urinalysis did not indicate any treatment-related effects. In the necropsy examination, the mean organ weights were not affected by the treatment. In the histopathology examination, there was an increased incidence of retinal atrophy for both sexes in the 500 and 1000 mg/kg treatment groups ((M) 0:1/60 vs. 500: 3/60, 1000: 6/60, (F) 0: 1/60 vs. 500: 6/60, 1000: 9/60); **Possible adverse effect:** increased incidence in retinal atrophy. **Chronic Dietary NOEL:** (M/F) 200 mg/kg/day (based upon the incidence of retinal atrophy noted for both sexes in the 500 mg/kg treatment group); **the test material did not demonstrate an oncogenic potential. Study acceptable.** (Moore, 6/1/06)

NEUROTOXICITY, RAT

**275-0458 227393 Brammer, A., "Chlorothalonil: 90-day dietary neurotoxicity study in rats," Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, 11/22/04. CTL No. PR1298. EPA MRID # 46526901. Twelve Alpk:APfSD (Wistar-derived) rat/sex/group were dosed in diet with Chlorothalonil, technical, purity 99.52% (Batch 3E10D1) for at least 90 days at 0, 30, 300, or 3000 ppm. Respective achieved dose levels were 0, 2.1, 22, or 232 mg/kg/day in males, and 0, 2.4, 24, and 243 mg/kg/day in females. NOEL = 300 ppm [discoloration of the skin and fur, staining around mouth and nose, reduced body weight (decrement of 18% in M and 6% in F: significant, $p < 0.01$ in males at weeks 2-14 and in females at weeks 2 and 5-14) and slightly reduced food consumption in both sexes]. Clinical signs noted above were most commonly observed during weeks 10-14. Overall session motor activity was significantly reduced in 3000 ppm females at week 14 only, but the pattern was one of normal accommodation and unlikely to reflect specific toxic response. Acceptable, with no adverse effects. Aldous, 10/27/06.

MISCELLANEOUS

112, 113 No record # No date Not chronic; FYI.

“105 to 108 No record # 6/24/83 Not chronic; FYI.

114 034400 7/3/85 Not chronic; FYI.

100, 114 034365 No date Not chronic; FYI.

100, 114 034461 No date Not chronic; FYI.

100, 114 034460 No date Not chronic; FYI.

122 046244 9/84 Guidance For The Reregistration Of Pesticide Products Containing Chlorothalonil As the Active Ingredient; EPA Registration Standard.

069 028411 8/17/82 Summary of Data Reported and Evaluation, Experimental data (N. A. C. A.): FYI; not a study; no review necessary. Davis.